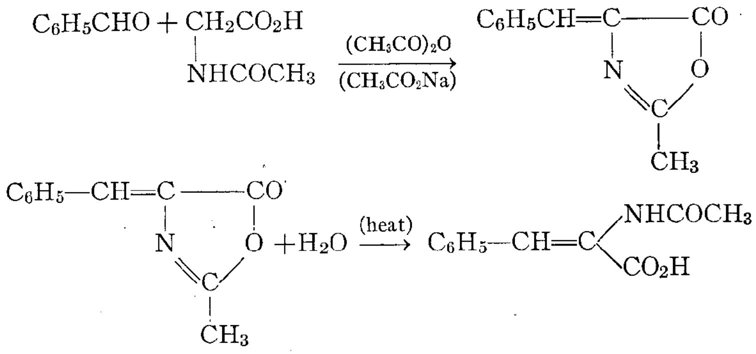
ORGANIC SYNTHESES

I

α-ACETAMINOCINNAMIC ACID



Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

A mixture of 58.5 g. (0.5 mole) of acetylglycine (p. 4) (Note 1), 30 g. (0.37 mole) of anhydrous sodium acetate, 75 cc. (79 g.; 0.74 mole) of freshly distilled benzaldehyde, and 134 g. (1.25 moles) of 95 per cent acetic anhydride in a loosely corked 1-l. Erlenmeyer flask is warmed on the steam bath with occasional stirring until solution is complete (ten to twenty minutes). The resulting solution is boiled for one hour under reflux, cooled, and placed in a refrigerator overnight. The solid mass of yellow crystals is treated with 125 cc. of cold water and broken up with a stirring rod. The crystals are then transferred to a Büchner funnel and washed thoroughly with cold water (Note 2). After being dried in a vacuum desiccator over phosphorus pentoxide and potassium hydroxide, the crude azlactone weighs 69–72 g.

(74–77 per cent of the theoretical amount). The product melts at 148–150°, and is sufficiently pure for preparative purposes (Note 3).

In a 1-l. round-bottomed, short-necked flask 47 g. (0.25 mole) of the crude azlactone of α-acetaminocinnamic acid is dissolved by boiling with a mixture of 450 cc. of acetone and 175 cc. of water. Hydrolysis is completed by boiling under reflux for four hours. Most of the acetone is then removed by distillation at ordinary pressure on a steam bath. The residual solution is diluted with 400 cc. of water, heated to boiling for five minutes to insure complete solution of the acetamino acid, and filtered (Notes 4 and 5). A small amount of undissolved material (0.2–0.5 g.) which remains on the filter is washed with 50–75 cc. of boiling water. Any crystals which separate from the filtrate are redissolved by heating, after which the solution is boiled for five minutes with 10 g. of Norite and filtered with the aid of gentle suction while still almost at the boiling point (Note 5). The Norite is washed thoroughly on the funnel with two to four 50-cc. portions of boiling water to remove the crystals which separate during the filtration, and the washings are added to the main filtrate. After standing in a refrigerator overnight the colorless, crystalline needles are collected on a Büchner funnel (Note 6), washed with 150–200 cc. of ice-cold water, and dried for several hours at 90–100°. The yield is 41–46 g. (80-90 per cent of the theoretical amount) of practically pure material, m.p. 191–192° (Note 7).

2. Notes

1. The azlactone of α-acetaminocinnamic acid may also be prepared by substituting the equivalent amount of glycine for acetylglycine and increasing the amount of acetic anhydride to three molecular proportions, but the yield is only about 45–50 per cent of the theoretical amount.

2. If the excess benzaldehyde is not almost completely removed by repeated washing with water, a final wash with 50–75 cc. of ether may be advantageous, although this causes some loss of azlactone owing to its solubility in ether.

3. The azlactone can be recrystallized from alcohol, carbon tetrachloride, or from ethyl acetate with addition of petroleum ether. Aqueous solvents should be avoided, since the azlactone ring is easily opened by water. When alcohol is used for recrystallization, there is some danger of opening the azlactone ring with the formation of an ester, particularly on prolonged heating of the solution.

4. The solution may be filtered by gravity through a large folded filter (preferably in a steam-jacketed funnel), or through a Büchner funnel with gentle suction.

5. The solubility of α-acetaminocinnamic acid in water decreases very rapidly on cooling below the boiling point of the solution. Since the solution is very nearly saturated with the product, a large share of the acid will crystallize in the funnel during filtration if the solution is allowed to cool too much. This property of the product makes it inadvisable to work with larger quantities.

6. Occasionally after treatment with Norite the solution is green owing to traces of iron and phenylpyruvic acid. If the crystals are still yellow at this point, the treatment with Norite should be repeated before the product is collected on a filter.

7. If further purification is desired, the product may be recrystallized from 600 cc. of boiling water, with a loss of about 5 per cent. The loss is due in part to hydrolysis of the product with the formation of phenylpyruvic acid.

3. Methods of Preparation

The azlactone of α-acetaminocinnamic acid has been prepared by heating a mixture of glycine, benzaldehyde, acetic anhydride, and anhydrous sodium acetate;[1,2] and from *N*-chloroacetylphenylalanine by treatment with acetic anhydride.[2]

α-Acetaminocinnamic acid has been prepared from the corresponding azlactone by hydrolysis with either aqueous sodium hydroxide[1] or with boiling water alone.[2]

[1] Erlenmeyer, Jr., and Früstück, Ann. **284**, 48 (1895).
[2] Bergmann and Stern, Ann. **448**, 26 (1926).

II

ACETYLGLYCINE

(Aceturic Acid)

$$H_2NCH_2CO_2H + (CH_3CO)_2O \rightarrow CH_3CONHCH_2CO_2H + CH_3CO_2H$$

Submitted by R. M. HERBST and D. SHEMIN.
Checked by REYNOLD C. FUSON and E. A. CLEVELAND.

1. Procedure

IN a 1-l. Erlenmeyer flask provided with a mechanical stirrer are placed 75 g. (1 mole) of glycine and 300 cc. of water. The mixture is stirred vigorously until the glycine is almost completely dissolved, when 215 g. (2 moles) of 95 per cent acetic anhydride (Note 1) is added in one portion. Vigorous stirring is continued for fifteen to twenty minutes, during which time the solution becomes hot and acetylglycine may begin to crystallize. The solution is placed in the refrigerator (Note 2) overnight to effect complete crystallization. The first crop of product is collected on a Büchner funnel, washed with ice-cold water, and dried at 100-110°. The first crop weighs 75–85 g. and melts at 207–208°. The combined filtrate and washings are evaporated to dryness under reduced pressure on a water bath at 50–60°. The residue on recrystallization from 75 cc. of boiling water yields a second fraction of 20–30 g. which melts at 207–208° after being washed with ice-cold water and dried at 100–110°. An additional 4–6 g. of only slightly less pure product may be obtained from the mother liquor by concentration. The total yield is 104–108 g. (89–92 per cent of the theoretical amount) (Note 3).

2. Notes

1. The equivalent quantity of 90 per cent acetic anhydride may be used.
2. The refrigerator used by the checkers maintained a temperature of 5–7°.
3. The method may be employed to acetylate most α-amino acids with only slight modifications depending upon the solubility of the particular amino acid. When optically active amino acids are acetylated, there is little or no racemization.[1]

3. Methods of Preparation

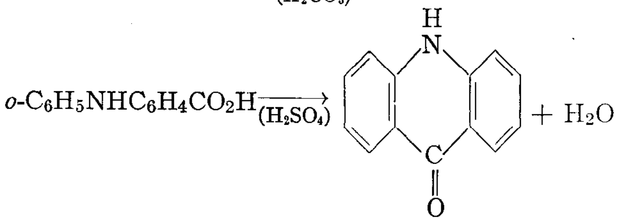
Acetylglycine has been prepared by the interaction of acetyl chloride and the silver salt of glycine in dry ether or benzene;[2,3] by the action of acetic anhydride on glycine suspended in warm benzene;[3] by heating glycine with acetic anhydride;[4] by treating an aqueous solution of glycine or its sodium salt with ketene;[5] and by treating an aqueous alkaline solution of glycine with acetic anhydride.[6]

[1] Behr and Clarke, J. Am. Chem. Soc. **54**, 1631 (1932).
[2] Kraut and Hartmann, Ann. **133**, 105 (1865).
[3] Curtius, Ber. **17**, 1665 (1884).
[4] Radenhausen, J. prakt. Chem. (2) **52**, 437 (1895).
[5] Bergmann and Stern, Ber. **63**, 437 (1930).
[6] Chattaway, J. Chem. Soc. **1931**, 2495.

III

ACRIDONE

$$o\text{-}ClC_6H_4CO_2H + C_6H_5NH_2 \xrightarrow[(K_2CO_3)]{(CuO)} o\text{-}C_6H_5NHC_6H_4CO_2H$$



Submitted by C. F. H. Allen and G. H. W. McKee.
Checked by W. W. Hartman and A. Weissberger.

1. Procedure

(*A*) *N-Phenylanthranilic Acid*.—In a 1-l. round-bottomed flask fitted with an air-cooled condenser, a mixture of 155 g. (1.66 moles) of aniline, 41 g. (0.26 mole) of *o*-chlorobenzoic acid (Note 1), 41 g. (0.30 mole) of technical, anhydrous potassium carbonate, and 1 g. of copper oxide is refluxed for two hours, using an oil bath. The excess aniline is removed by distillation with steam (about three hours is required), and 20 g. of decolorizing carbon (Note 2) is added to the brown residual solution. The mixture is boiled for fifteen minutes and filtered by suction. The filtrate is added, with stirring, to a mixture of 30 cc. of concentrated hydrochloric acid and 60 cc. of water. The precipitated acid is filtered with suction when cold. After drying to constant weight in the air, the yield is 46–52 g. (82–93 per cent of the theoretical amount) of a nearly white product; m.p. 179–181° with preliminary shrinking (Notes 3, 4, 5).

(*B*) *Acridone*.—In a 500-cc. flask a solution of 42.7 g. (0.2 mole) of *N*-phenylanthranilic acid (Note 6) in 100 cc. of concentrated sulfuric acid (sp. gr. 1.84) is heated on a boiling water bath for four hours, and then poured into 1 l. of boiling water. Spattering is minimized by allowing the solution to run down the wall of the container. The yellow precipitate is filtered after boiling for five minutes, and the filtrate saved (Note 7). The moist solid is boiled for five minutes with a solution of 30 g. (0.28 mole) of sodium carbonate in 400 cc. of water, collected with suction (Note 8), and washed well with water. After drying in the air the crude acridone weighs 35.5–37.5 g. (91–96 per cent of the theoretical amount) and melts at 344–346° (Note 9). This material is pure enough for many purposes; it may be recrystallized from a mixture of aniline and acetic acid, using 10 cc. of aniline and 25 cc. of acetic acid for every 2 g. of solid. The recovery is about 90 per cent, and the recrystallized product melts at 348–352° (Note 10).

2. Notes

1. The technical grade of *o*-chlorobenzoic acid (60 g.) is dissolved in 200 cc. of hot water containing 20 g. of sodium carbonate, 10 g. of decolorizing carbon is added, and, after boiling for ten minutes, the mixture is filtered by suction. The filtrate is added to hydrochloric acid prepared by diluting 31 cc. of the concentrated acid with an equal volume of water. The air-dried product weighs 41 g. and is used directly. This purification is essential to obtain a good yield and a product of good quality. If it is omitted, a blue to black acid results, from which the color is removed only with difficulty.

2. Ordinary animal charcoal and Darco gave equally good results.

3. *N*-Phenylanthranilic acid decomposes slowly at elevated temperatures. Before the melting point is reached, there is considerable preliminary shrinkage. If the "dip method" is used,

the melting point is 182–183°. The literature values vary from 181° to 184° for the pure acid.

4. This acid is pure enough for all ordinary purposes. The melting point is only slightly raised by dissolving 5 g. in 100 cc. of water containing 2.5 g. of sodium carbonate, adding 2.5 g. of decolorizing carbon, boiling for five minutes, filtering, and acidifying. The recovery is 4.6 g. If the product is colored this procedure must be followed to get acridone of light color.

5. For recrystallization, 5 g. of the acid is dissolved in 25 cc. of boiling alcohol and 5 cc. of water added. The recovery is 4.8 g., and the melting point is 182–183°. Acetic acid (2 cc. per gram) may be substituted for alcohol; it is more convenient for recrystallizing large quantities.

6. The *N*-phenylanthranilic acid may be used without recrystallization if it has been prepared from purified *o*-chlorobenzoic acid. If not, the crude *N*-phenylanthranilic acid must be submitted to the decolorizing treatment described in Note 4, as otherwise a greenish acridone is obtained, which, however, has the same melting point.

7. On standing overnight, the filtrate deposits 1.6 to 2 g. of a very impure product which melts at about 315°.

8. On acidification of the filtrate, a little (1.5–2 g.) *N*-phenylanthranilic acid is always precipitated.

9. The crude acridone shrinks in a capillary tube at 330–335° and melts to a dark-colored liquid at 344–346°.

10. *iso*-Amyl alcohol may also be used for recrystallization; 1 g. of acridone requires 120 cc. of solvent and yields 0.75 g. of material melting at 354°, using a Berl-Kullman copper block.[1]

3. Methods of Preparation

The practical methods of preparation of *N*-phenylanthranilic acid are the action of aniline on *o*-chloro- or *o*-bromobenzoic acid,[2,3] or the action of bromobenzene on anthranilic acid,[4,5,6] using copper or its salts in both instances.

The only method of preparative value for acridone is by ring closure of *N*-phenylanthranilic acid.[7]

[1] Berl and Kullman, Ber. **60**, 811 (1927); for an elaborate modification, see Walsh, Ind. Eng. Chem. Anal. Ed. **6**, 468 (1934).

[2] Ullmann, Ber. **36**, 2383 (1903); Ann. **355**, 322 (1907).

[3] Ger. pat. 145,189 [Chem. Zentr. **1903**, II, 1097].

[4] Goldberg, Ber. **39**, 1691 (1906).

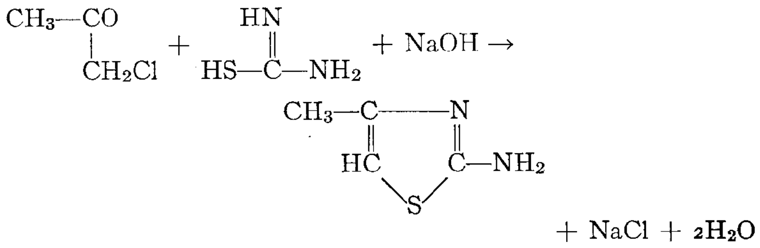
[5] Houben, ibid. **39**, 3238 (1906).

[6] Ger. pat. 173,523 [Chem. Zentr. **1906**, II, 931]; Ger. pat. 187,870 [Chem. Zentr. **1907**, II, 1465].

[7] Graebe, Ber. **25**, 1734 (1892); Ann. **276**, 35 (1893); Matsumura, J. Am. Chem. Soc. **57**, 1533 (1935).

IV

2-AMINO-4-METHYLTHIAZOLE



Submitted by J. R. Byers and J. B. Dickey.
Checked by L. F. Fieser and Byron Riegel.

1. Procedure

Seventy-six grams (1 mole) of thiourea is suspended in 200 cc. of water (Note 1) in a 500-cc. flask equipped with a reflux condenser, dropping funnel, and mechanical stirrer. The stirrer is started, and 92.5 g. (1 mole) of chloroacetone (Note 2) is run in during thirty minutes. As the reaction proceeds the thiourea dissolves and the temperature rises. The yellow solution is refluxed for two hours and cooled, and, while the mixture is stirred continuously but not so rapidly as to produce a troublesome emulsion, 200 g. of solid sodium hydroxide is added with cooling. The upper, oily layer is separated in a separatory funnel and the aqueous layer is extracted three times with ether, using a total of 300 cc. (Note 3). The dark red oil is combined with the ethereal extract, and the solution is dried over 30 g. of solid sodium hydroxide and filtered by gravity to remove small amounts of tar. The ether is removed by distillation from a steam bath, and the oil is distilled at reduced pressure. After a very small fore-run, the 2-amino-4-methylthiazole is collected

at 117–120°/8 mm., or 130–133°/18 mm. The yield of material melting at 44–45° is 80–85.5 g. (70–75 per cent of the theoretical amount).

2. Notes

1. The reaction may be conducted without this diluent, but it is then likely to become violent.
2. Commercial chloroacetone was distilled and the fraction boiling at 116–122° taken; nearly all of this boiled at 118–120°.
3. If a precipitate is produced and causes an emulsion, it is well to add ice and water until this dissolves.

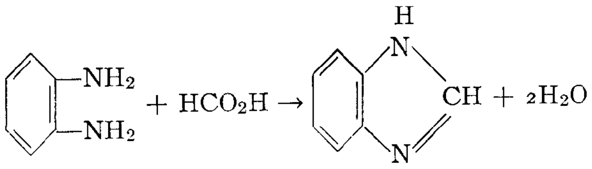
3. Methods of Preparation

The method given is essentially that of Traumann.[1] 2-Amino-4-methylthiazole has been prepared also from chloroacetone and ammonium thiocyanate,[2] from chloroacetone and ammonium thiocyanate in ammonia water,[3] by the action of ammonium thiocyanate on thiocyanoacetone,[3] by saponifying and decarboxylating the cyclic ester from ethyl γ-bromoacetoacetate and thiourea,[4] and from thiocyanoacetone and ammonia in absolute ether.[5]

[1] Traumann, Ann. **249**, 37 (1888).
[2] Hantzsch and Traumann, Ber. **21**, 938 (1888); Hantzsch and Weber, ibid. **20**, 3118 (1887).
[3] Tscherniac and Norton, ibid. **16**, 345 (1883); Tscherniac, J. Chem. Soc. **115** 1071 (1919).
[4] Steude, Ann. **261**, 33 (1891).
[5] Hantzsch, Ber. **61**, 1785 (1928).

V

BENZIMIDAZOLE



Submitted by E. C. WAGNER and W. H. MILLETT.
Checked by W. W. HARTMAN and G. W. SAWDEY.

1. Procedure

IN a 500-cc. round-bottomed flask 54 g. (0.5 mole) of *o*-phenylenediamine (p. 70) (Note 1) is treated with 32 cc. (34.6 g.) of 90 per cent formic acid (0.75 mole) (Note 2). The mixture is heated in a water bath at 100° for two hours. After cooling, 10 per cent sodium hydroxide solution is added slowly, with thorough mixing by rotation of the flask, until the mixture is just alkaline to litmus. The crude benzimidazole is collected with suction in a 75-mm. Büchner funnel; ice-cold water is used to rinse all solid out of the reaction flask. The crude product is pressed thoroughly on the filter, washed with about 50 cc. of cold water, and then purified without previous drying (Note 3).

The benzimidazole is dissolved in 750 cc. of boiling water in a 1500-cc. beaker. The solution is digested for fifteen minutes with about 2 g. of decolorizing carbon (Norite) and filtered rapidly through a well-heated filter (Note 4). The filtrate is cooled to 10–15°, and the benzimidazole is filtered and washed with 50 cc. of cold water. The white (Note 5) product is dried at 100°. The melting point is 170–172°, and the yield is 49–50.5 g. (83–85 per cent of the theoretical) (Notes 6 and 7).

2. Notes

1. The *o*-phenylenediamine used was a good grade of commercial material, m.p. 99–101°. The hydrochloride can be used with or without addition of sodium formate.

2. The yield is not greatly affected if the amount of formic acid is decreased almost to the theoretical, but a safe excess is recommended to insure utilization of the *o*-phenylenediamine. Formic acid of considerably less than 90 per cent concentration will form benzimidazole; good yields were obtained with 40 per cent acid.

3. The crude benzimidazole, if dried at 100°, weighs 57.5–59 g. (97–99 per cent of the theoretical), melts at 167–168°, and is yellow tinged. This discoloration is hard to remove and persists after two crystallizations (Note 5).

4. The solution is almost saturated when boiling, and crystallization begins at once on cooling. The filter must be thoroughly heated and filtration must be rapid, or crystallization will occur in the filter.

5. If the crystallized benzimidazole is discolored, the following treatment will yield a good product. The benzimidazole is dissolved in boiling water (13 cc. per gram), and a strong solution of potassium permanganate is added until the liquid becomes opaque owing to the precipitated brown oxide of manganese. To the hot mixture solid sodium bisulfite is added until clarification results. Decolorizing carbon is introduced, and the mixture is digested for fifteen minutes and filtered hot. The recovery is 90–92 per cent.

6. A small additional amount (2–2.5 g.) can be obtained by evaporation of the mother liquor to about 30 cc.

7. This is a general method of preparing benzimidazoles. Using an equivalent of acetic acid (45 g.) in place of formic acid, 2-methylbenzimidazole, m.p. 172–174°, can be prepared in 68 per cent yield.

3. Methods of Preparation

Benzimidazole has been prepared from *o*-phenylenediamine by the action of chloroform and alcoholic potassium hydroxide [1] and of formic acid,[2] and by the reduction of *o*-nitroformanilide.[3] Less serviceable methods include the interaction of *o*-phenylenediamine and dichloromethylformamidine [4] or formoacetic anhydride,[5] and the thermal decarboxylation of benzimidazole-2-carboxylic acid.[6] The procedure described was developed [7] from that of Wundt.[2]

The conversion of aliphatic acids to 2-alkylbenzimidazoles, by heating with *o*-phenylenediamine, has been proposed as a general method for preparing solid derivatives for identification.[8]

[1] Grassi-Cristaldi and Lambardi, Gazz. chim. ital. **25**, 225 (1895).

[2] Wundt, Ber. **11**, 826 (1878); Heller and Kuhn, ibid. **37**, 3116 (1904); Pauly and Gundermann, ibid. **41**, 4012 (1908).

[3] Niementowski, ibid. **43**, 3018 (1910).

[4] Dains, ibid. **35**, 2503 (1902).

[5] Béhal, Ger. pat. 115,334 [Frdl. **6**, 1280 (1900)].

[6] Bistrzycki and Przeworski, Ber. **45**, 3489 (1912).

[7] Wagner and Simons, J. Chem. Education **13**, 267 (1936).

[8] Seka and Müller, Monats. **57**, 97 (1931); Pool, Harwood and Ralston, J. Am. Chem. Soc. **59**, 178 (1937).

VI

BENZOHYDROXAMIC ACID

$$C_6H_5CO_2C_2H_5 + H_2NOH + KOH \rightarrow C_6H_5CONHOK + C_2H_5OH + H_2O$$

$$C_6H_5CONHOK + CH_3CO_2H \rightarrow C_6H_5CONHOH + CH_3CO_2K$$

Submitted by C. R. Hauser and W. B. Renfrow, Jr.
Checked by C. R. Noller and M. Synerholm.

1. Procedure

(*A*) *Potassium Benzohydroxamate.*—Separate solutions of 46.7 g. (0.67 mole) of hydroxylamine hydrochloride in 240 cc. of methyl alcohol, and of 56.1 g. (1 mole) of c.p. potassium hydroxide in 140 cc. of methyl alcohol, are prepared at the boiling point of the solvent. Both are cooled to 30–40° (Note 1), and the one containing alkali is added with shaking to the hydroxylamine solution; any excessive rise of temperature during the addition is prevented by occasional cooling in an ice bath. After all the alkali has been added, the mixture is allowed to stand in an ice bath for five minutes to insure complete precipitation of potassium chloride. Fifty grams (0.33 mole) of ethyl benzoate is added with thorough shaking, and the mixture filtered immediately with suction. The residue in the funnel is washed with a little methyl alcohol. The filtrate is placed in an Erlenmeyer flask and allowed to stand at room temperature. Crystals begin to form within twenty minutes to three hours, depending upon the amount of supersaturation of the solution. After forty-eight hours the crystals are filtered, washed with a little absolute ethyl alcohol, and dried in air. The yield is 33–35 g. (57–60 per cent of the theoretical amount). (Notes 2, 3, and 4.)

(*B*) *Benzohydroxamic Acid.*—A mixture of 35 g. (0.2 mole) of the potassium salt in 160 cc. of 1.25 *N* acetic acid is stirred and heated until a clear solution is obtained. The solution is allowed to cool to room temperature and finally chilled in an ice bath. Benzohydroxamic acid separates as white crystals. After filtering and drying the product melts at 120–128° and weighs 25–26 g. (92–95 per cent of the theoretical amount). The crude material may be purified by dissolving it in 4.5 times its weight of hot ethyl acetate, filtering from a small amount of solid, and allowing the solution to cool to room temperature. The white crystals which separate are filtered, washed with a little benzene, and allowed to dry in air. The yield of recrystallized product, m.p. 125–128°, from 26 g. of crude material is 20 g. (77 per cent recovery) (Note 5).

2. Notes

1. The hydroxylamine hydrochloride solution should not be cooled too quickly or crystallization may occur before mixing. Exposure to atmospheric oxygen should be minimized after mixing the solutions, to avoid oxidation of the free hydroxylamine.

2. By concentrating the alcoholic mother liquors an additional 3–5 g. of the potassium salt may be obtained.

3. This salt can be used for the preparation of acyl derivatives; for example, when suspended in dioxane and treated with benzoyl chloride, dibenzohydroxamic acid is formed in excellent yield.[1]

4. The potassium salts of *p*-methyl- and *p*-methoxybenzohydroxamic acid have been prepared by the submitters by this method in approximately the same yields.

5. This product has a neutralization equivalent of 137.5–138 (calculated 137.1) when determined as follows. Several drops of an alcoholic solution of 1,3,5-trinitrobenzene are added to 30–40 cc. of water in a flask, and 0.1 *N* alkali (about 0.5 cc.) run in until a pink color is just produced. An accurately weighed sample (approximately 0.3 g.) of benzohydroxamic acid is then dissolved in the solution and titrated with standard alkali until the pink color is restored. The latter titer is used to calculate the neutralization equivalent.

3. Methods of Preparation

Benzohydroxamic acid has been prepared by the action of hydroxylamine on benzoyl chloride,[2] ethyl benzoate,[1,3] or benzamide.[4]

1 Renfrow and Hauser, J. Am. Chem. Soc. **59**, 2312 (1937).

2 Lossen, Ann. **161**, 347 (1872); Jones and Hurd, J. Am. Chem. Soc. **43**, 2446 (1921).

3 Tiemann and Krüger, Ber. **18**, 740 (1885); Jeanrenaud, ibid. **22**, 1272 (1889).

4 Hofmann, ibid. **22**, 2856 (1889).

VII

ε-BENZOYLAMINO-α-BROMOCAPROIC ACID

$$3C_6H_5CONH(CH_2)_5CO_2H + 3Br_2 + PBr_3 \rightarrow 3C_6H_5CONH(CH_2)_4\underset{\underset{\displaystyle Br}{|}}{C}HCOBr + P(OH)_3 + 3HBr$$

$$C_6H_5CONH(CH_2)_4\underset{\underset{\displaystyle Br}{|}}{C}HCOBr \xrightarrow{H_2O} C_6H_5CONH(CH_2)_4\underset{\underset{\displaystyle Br}{|}}{C}HCO_2H$$

Submitted by J. C. Eck and C. S. Marvel.
Checked by C. R. Noller and William Munich.

1. Procedure

An intimate mixture of 150 g. (0.64 mole) of dry ε-benzoylaminocaproic acid (p. 20) and 26.4 g. (0.85 gram atom) of dry red phosphorus is placed in a 1-l. three-necked flask provided with a separatory funnel, an air-cooled condenser connected through a calcium chloride tube to a water trap, and a mechanical stirrer (Note 1). The reaction flask is surrounded by an ice-salt mixture, the stirrer started, and 408 g. (131 cc.; 2.55 moles) of dry bromine added dropwise from the separatory funnel. When all the bromine has been added, the cooling bath is removed. The mixture is warmed slowly at first and finally heated on a steam bath, with stirring, until the bromine vapors have practically disappeared. The hot mixture is poured slowly into 400 cc. of water in a 1-l. beaker with hand stirring. The viscous acid bromide reacts with the water with the evolution of heat, and the solid acid is formed. The lumps are pulverized, the mixture is replaced in the original reaction flask, and the whole treated with a slow stream of sulfur dioxide to remove excess bromine. The solid product is filtered on a Büchner funnel, washed with

three 50-cc. portions of water, and air dried. The crude material is dissolved in 250 cc. of hot 95 per cent alcohol, filtered, and poured with stirring into 1 l. of cold water (Note 2). After filtering and air drying there is obtained 130–180 g. (64–89 per cent of the calculated amount) of acid melting at 162–165°.

2. Notes

1. The stirrer must be very powerful because the mixture becomes lumpy and finally very viscous. If the material agglomerates so badly that the stirrer will not operate, hand stirring may be necessary temporarily until the mass liquefies sufficiently to renew mechanical stirring. The checkers tried one run in which carbon tetrachloride was added to facilitate stirring, but, though it accomplished this purpose, the yield was only about half of that obtained without a liquid medium.

2. The crude product may be recrystallized from ethyl alcohol, but the melting point is the same as that of the product obtained by precipitation with water, and the yield is considerably less.

3. Method of Preparation

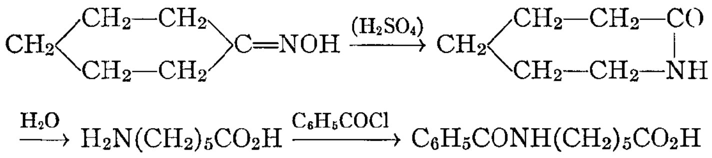
The above procedure [1] is essentially that of Braun.[2]

[1] Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).

[2] Braun, Ber. **42**, 839 (1909).

VIII

ε-BENZOYLAMINOCAPROIC ACID



Submitted by J. C. Eck and C. S. Marvel.
Checked by C. R. Noller and William Munich.

1. Procedure

(*A*) *Cyclohexanoneoxime*.—In a 5-l. flask fitted with an efficient mechanical stirrer and an 8-mm. glass inlet tube reaching to within 5 cm. of the bottom of the flask, are placed 1.5 kg. of cracked ice and a solution of 182 g. (2.5 moles) of technical sodium nitrite (95 per cent) in 500 cc. of water (Note 1). The flask is placed in an ice-salt mixture, and a cold (−8°) solution of sodium bisulfite, prepared by saturating with sulfur dioxide a solution of 143 g. (1.35 moles) of anhydrous sodium carbonate in 600 cc. of water, is added. While the temperature is kept below 0°, a moderate stream of sulfur dioxide is passed into the mixture until it is acid to Congo red and then just enough longer to remove the dark color which appears shortly before the solution becomes acid.

To this solution are added 196 g. (2 moles) of technical cyclohexanone and 500 cc. of 85 per cent ethyl alcohol; the cooling bath is replaced by a steam bath, the stirrer started, and the mixture heated to 75°. The flask is then packed in mineral wool or other insulating material and allowed to cool slowly, with effective stirring, for forty-eight hours. The solution at room temperature is exactly neutralized to litmus with a 50 per cent solu-

tion of sodium hydroxide, with cooling and stirring. About 330 g. of sodium hydroxide solution is required.

The oily layer is separated and the aqueous solution extracted with two 200-cc. portions of ether. The oil and ether extracts are combined, the ether is removed, and the residue distilled from a 500-cc. modified Claisen flask having a 25-cm. fractionating side arm. The fraction boiling at 95–100° at 5 mm. weighs 170–190 g. and melts at 78–80°. This product is transferred to a large mortar, allowed to cool, and ground with 120 cc. of petroleum ether (b.p. 35–60°). After filtering with suction, and allowing the solvent to evaporate from the crystals, there is obtained 133–147 g. of cyclohexanoneoxime (59–65 per cent of the calculated amount) melting at 86–88° (Note 2).

(*B*) *ε-Benzoylaminocaproic Acid*.—The rearrangement of 100 g. (0.88 mole) of pure cyclohexanoneoxime (Note 3) is carried out in the following way. In a 1-l. beaker are placed a 10-g. portion of the oxime and 20 cc. of 85 per cent sulfuric acid (sp. gr. 1.783) (Note 4). The beaker is heated with a low flame and the contents mixed with a rotary motion until bubbles first appear. The beaker is then removed from the flame immediately, and the violent reaction, which lasts a few seconds, is allowed to subside. The acid solution of ε-caprolactam is transferred to a 5-l. round-bottomed flask, and another 10-g. portion of the oxime is placed in the beaker and rearranged with sulfuric acid as before. The combined acid solution from the ten operations is diluted with 2.5 l. of water and boiled gently for one and one-half hours with 5 g. of decolorizing carbon. The solution is filtered and exactly neutralized to litmus with 50 per cent sodium hydroxide solution. About 510 g. of sodium hydroxide solution is usually required. The neutral solution is boiled for one-half hour with 5 g. of decolorizing carbon and filtered.

The filtrate is placed in a 5-l. flask fitted with a mechanical stirrer, cooled in an ice bath to 10°, and a solution of 55 g. (1.37 moles) of sodium hydroxide in 55 cc. of water added. Keeping the temperature at 10°, 94 g. (0.67 mole) of benzoyl chloride is added dropwise from a separatory funnel over a period of thirty-five to forty minutes, with rapid stirring. The

mixture is stirred for an hour longer, filtered, and placed in a 4-l. beaker. The cold filtrate is slowly acidified to Congo red by adding 10 per cent hydrochloric acid, with hand stirring (about 450 cc. of acid is required). The solid (Note 5) is filtered with suction, washed with water, and spread out to dry. When dry, the product is washed with two 100-cc. portions of petroleum ether (35–60°) to remove the admixed benzoic acid. The adhering petroleum ether is allowed to evaporate from the crystals, and the final drying is carried out in a vacuum desiccator over sulfuric acid. The yield of purified product, m.p. 77–80°, is 135–150 g. (65–72 per cent of the calculated amount, based on cyclohexanoneoxime).

2. Notes

1. The sodium nitrite may be added directly to 2 kg. of ice, but if this is done, the nitrite and ice should be mixed thoroughly outside of the flask to prevent caking of the ice.

2. Cyclohexanoneoxime can be prepared in somewhat better yields by the standard procedure (Org. Syn. **11**, 56) but at increased cost because of the high price of hydroxylamine hydrochloride.

3. The rearrangement of the oxime is carried out in 10-g. portions and in a large open beaker because of the violence of the reaction. It is essential to use oxime of good quality or a product of inferior grade results.

4. Acid of this concentration may be prepared by mixing five volumes of concentrated sulfuric acid with one volume of water.

5. If the acid separates as an oil, it should be allowed to stand with occasional stirring until it solidifies.

3. Methods of Preparation

ε-Benzoylaminocaproic acid has been prepared by treatment of benzoylpiperidine with phosphorus pentachloride to form ε-benzoylaminoamyl chloride, conversion to the nitrile, and

hydrolysis to the acid.[1] The above procedure from cyclohexanoneoxime has been published recently.[2] Methods for the isolation of ε-caprolactam and ε-aminocaproic acid have appeared in an earlier volume of this series.[3]

[1] Braun, Ber. **42**, 839 (1909).
[2] Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).
[3] Org. Syn. **17**, 60 and 7.

IX

ω-BROMOACETOPHENONE

(Phenacyl Bromide)

$$C_6H_5COCH_3 + Br_2 \xrightarrow{(AlCl_3)} C_6H_5COCH_2Br + HBr$$

Submitted by R. M. Cowper and L. H. Davidson.
Checked by Lee Irvin Smith and E. W. Kaiser.

1. Procedure

A solution of 50 g. (49 cc., 0.42 mole) of acetophenone in 50 cc. of pure anhydrous ether (Note 1) is placed in a dry three-necked flask fitted with a separatory funnel, mechanical stirrer, and reflux condenser (Note 2). The solution is cooled in an ice bath, 0.5 g. of anhydrous aluminum chloride is introduced (Note 3), and 67 g. (21.5 cc., 0.42 mole) of bromine is added gradually from the separatory funnel, with stirring, at the rate of about 1 cc. per minute. The bromine color disappears rapidly although very little hydrogen bromide is evolved; towards the end of the reaction the solution becomes pink in color.

After the bromine has been added the ether and dissolved hydrogen bromide are removed at once (Note 4) under reduced pressure with a slight current of air. The phenacyl bromide remains as a solid mass of brownish-yellow crystals (Note 5); the color is removed by shaking with a mixture of 10 cc. of water and 10 cc. of petroleum ether. The crystals are filtered with suction and washed several times with fresh portions of the solvent mixture, if necessary, until a white product is obtained (Notes 6 and 7). The crude phenacyl bromide weighs 74–80 g. (88–96 per cent of the theoretical amount) and melts at 45–48°. This material is sufficiently pure for many purposes. If higher

purity is desired the crude product may be recrystallized from methanol (25–30 cc.) and yields 54–55 g. (64–66 per cent of the theoretical amount) of white crystals melting at 49–51° (Notes 7 and 8).

2. Notes

1. Dry carbon tetrachloride may be used as a solvent but is less favorable than dry ether.

2. Quantities up to 200 g. of acetophenone may be brominated in a single operation with equally good yields, but this is not generally advisable unless the product is to be used at once, since it becomes discolored on standing.

3. Without aluminum chloride the reaction is slow and incomplete.

4. If the ether and hydrogen bromide are not removed immediately the solution blackens on standing and a lower yield of less pure product results.

5. Phenacyl bromide is a lachrymator and should be manipulated carefully, to avoid contact with the skin and inhalation of the vapor.

6. The water removes yellow color due to residual hydrogen bromide, and the petroleum ether removes unchanged acetophenone or oily by-product. Since the product is quite insoluble in water and only slightly soluble in cold petroleum ether, it may be washed several times with little loss.

7. The checkers observed that all specimens of the product, even after recrystallization, although white at first, became dark and discolored on standing in a vacuum desiccator (over calcium chloride).

8. Phenacyl bromide is a useful reagent for the identification of organic acids by conversion to crystalline phenacyl esters.[1,2]

3. Methods of Preparation

ω-Bromoacetophenone has been prepared by the bromination of acetophenone in carbon disulfide,[3,5] in acetic acid,[1,4,5] and in other organic solvents.[4] The quantitative aspects of the bromination in various solvents have been investigated by Kröhnke.[5]

The use of ether in the present method is based on the use of this solvent for the bromination of desoxybenzoin (phenylacetophenone).[6]

[1] Rather and Reid, J. Am. Chem. Soc. **41**, 77 (1919).
[2] Shriner and Fuson, "The Systematic Identification of Organic Compounds," pp. 95 and 144, John Wiley & Sons, New York, 1935.
[3] Emmerling and Engler, Ber. **4**, 148 (1871); Hunnius, ibid. **10**, 2007 (1877); Staedel, ibid. **13**, 837 (1880), **16**, 22 (1883); Bottinger, ibid. **14**, 1238 (1881).
[4] Mohlau, ibid. **15**, 2465 (1882); Lazennac, Bull. soc. chim. (4) **5**, 501 (1909).
[5] Kröhnke, Ber. **69**, 921 (1936).
[6] Limpricht and Schwanert, Ann. **155**, 68 (1870).

X

n-BUTYL SULFATE

$$(C_4H_9)_2SO_3 + SO_2Cl_2 \rightarrow C_4H_9OSO_2Cl + C_4H_9Cl + SO_2$$
$$C_4H_9OSO_2Cl + (C_4H_9)_2SO_3 \rightarrow (C_4H_9)_2SO_4 + C_4H_9Cl + SO_2$$

Submitted by C. M. Suter and H. L. Gerhart.
Checked by C. R. Noller and M. Synerholm.

1. Procedure

In a 2-l. three-necked flask fitted with a dropping funnel, mercury-sealed stirrer, and condenser, is placed 625 g. (3.22 moles) of *n*-butyl sulfite (p. 29). The condenser is connected to a gas-absorption trap, and 217 g. (131 cc., 1.61 moles) of sulfuryl chloride (Note 1) is added over a period of thirty minutes, with rapid stirring and cooling with tap water. The dropping funnel is then replaced by a thermometer dipping into the liquid and the flask is heated slowly, with stirring, until the refluxing of the butyl chloride becomes vigorous (about 100–110°). Sulfur dioxide is evolved copiously during this time. The condenser is replaced with a 40-cm. Vigreux column and downward condenser, and the temperature gradually raised to 130–135° and kept there until no more sulfur dioxide or butyl chloride distils. The heating and distillation require about two hours. The residue of crude *n*-butyl sulfate is cooled to room temperature, and 100 cc. of saturated sodium carbonate solution is added. The mixture is stirred for about ten minutes, poured into a separatory funnel, and let stand for thirty minutes to allow the layers to separate. The upper layer is dried with calcium chloride, at least overnight, and then allowed to stand over 15 g. of anhydrous sodium or potassium carbonate for a day, with occasional shaking. The

product is filtered into a 500-cc. modified Claisen flask with a 25-cm. fractionating sidearm, and distilled from an oil bath. The first distillation gives 250–280 g. (74–83 per cent of the calculated amount) of *n*-butyl sulfate, b.p. 110–114° at 4 mm., which has a sharp odor. Redistillation gives a pure material with a slight ester odor, boiling at 109–111° at 4 mm., with only a small mechanical loss (Note 2).

2. Notes

1. Commercial sulfuryl chloride was redistilled and the fraction boiling at 69–70° was used.
2. The submitters report that *n*-propyl sulfate may be prepared in similar fashion, the yield being about 66–70 per cent. The second distillation in this case should be done through a short column to remove higher-boiling material; *n*-propyl sulfate distils at 88–91° at 4 mm.

3. Methods of Preparation

n-Butyl sulfate has been prepared by the action of *n*-butyl chlorosulfonate upon *n*-butyl orthoformate or *n*-butyl sulfite.[1] It has been obtained also by oxidation of *n*-butyl sulfite with potassium permanganate in glacial acetic acid solution.[2] The method described above appears to be the most satisfactory for laboratory-scale preparations.

[1] Levaillant, Compt. rend. **197**, 648 (1933); Barkbenbus and Owen, J. Am Chem. Soc., **56**, 1204 (1934).

[2] Evans, Ph.D. Dissertation, Northwestern University, 1935.

XI

n-BUTYL SULFITE

$$2C_4H_9OH + SOCl_2 \rightarrow (C_4H_9)_2SO_3 + 2HCl$$

Submitted by C. M. Suter and H. L. Gerhart.
Checked by C. R. Noller and M. Synerholm.

1. Procedure

In a 2-l. three-necked flask fitted with a mercury-sealed stirrer, thermometer, condenser, and dropping funnel, is placed 684 g. (845 cc., 9.24 moles), of dry *n*-butyl alcohol (Note 1). The condenser is connected to a trap for absorbing hydrogen chloride, and 500 g. (4.2 moles) of thionyl chloride (Note 2) is added over a period of two hours, with stirring. The reaction mixture is kept at 35–45°, by immersing the flask in ice water, during the addition of the first half of the thionyl chloride (Note 3). After evolution of hydrogen chloride begins, the water bath is removed and a small flame applied to maintain this temperature. After all the thionyl chloride has been added the temperature is raised gradually to the boiling point, over a period of thirty minutes, to complete the reaction and remove the remainder of the hydrogen chloride. The reaction mixture is then transferred to a 1-l. modified Claisen flask with a 25-cm. fractionating side arm, and fractionated under diminished pressure. After a fore-run consisting largely of unchanged alcohol, there is obtained 625–689 g. (77–84 per cent of the calculated amount) of *n*-butyl sulfite, b.p. 109–115° at 15 mm. Refractionation gives 585–674 g. (72–82 per cent) of a product distilling at 109–112° at 14 mm. (Note 4).

2. Notes

1. Commercial *n*-butyl alcohol was dried by distillation through a column; the fore-run and a small fraction collected after the vapors reached 117° were discarded.

2. Commercial thionyl chloride was redistilled, and the fraction boiling at 78–80° was employed.

3. Considerable heat is evolved until gas evolution begins, after which heat is absorbed.

4. The submitters report that *n*-propyl sulfite is obtained from *n*-propyl alcohol in somewhat smaller yields, by the same procedure.

3. Methods of Preparation

The method used is essentially that of Voss and Blanke.[1] *n*-Butyl sulfite has also been made by the action of sulfur chloride on butyl alcohol.[2]

[1] Voss and Blanke, Ann. **485**, 258 (1931); Barkenbus and Owen, J. Am. Chem Soc. **56**, 1204 (1934).

[2] Bert, Compt. rend. **178**, 1827 (1924).

XII

COPPER CHROMITE CATALYST

(Copper-Chromium Oxide)

$$\begin{array}{l} Cu(NO_3)_2 \\ Ba(NO_3)_2 \\ (NH_4)_2CrO_4 \end{array} \longrightarrow \left[\begin{array}{l} \text{Complex} \\ \text{Chromates} \end{array}\right] \xrightarrow{\text{ignition}} \begin{array}{l} CuCr_2O_4 \\ BaCr_2O_4 \\ \text{(Note 1)} \end{array}$$

Submitted by W. A. Lazier and H. R. Arnold.
Checked by R. L. Shriner and J. F. Kaplan.

1. Procedure

A MIXTURE of 26 g. (0.1 mole) of C.P. barium nitrate and 800 cc. of distilled water is warmed to 70°. After solution is complete 218 g. (0.9 mole) of C.P. cupric nitrate trihydrate is added and the mixture stirred at 70° until a clear solution results (Note 2).

A solution of ammonium chromate is prepared by dissolving 126 g. (0.5 mole) of C.P. ammonium dichromate in 600 cc. of distilled water and adding 150 cc. of 28 per cent aqueous ammonia (sp. gr. 0.9) (Note 3). The warm solution of the nitrates is stirred (hand stirring is adequate) while the ammonium chromate solution is poured into it in a thin stream. The stirring is continued for a few minutes, after which the reddish brown precipitate of copper barium ammonium chromate is collected (Note 4) and pressed in a 16-cm. Büchner funnel, and dried at 110°. This dry precipitate is placed in a loosely covered nickel pan (Note 5), or one or two small porcelain casseroles covered with watch glasses, and heated in a muffle furnace for one hour at 350–450° (Note 6). At this point the yield of chromite should be about 160 g. The ignition residue is pulverized in a mortar to break up any hard lumps that may be present (Note 7) and

then transferred to a 2-l. beaker containing 1200 cc. of 10 per cent acetic acid. After being stirred for ten minutes the mixture is allowed to settle. After about ten minutes, two-thirds or more of the spent acid solution is decanted and replaced by 1200 cc. of fresh 10 per cent acetic acid, and the extraction repeated. The residue is washed by repeating the extraction procedure four times with 1200 cc. of distilled water each time (Note 8). The insoluble portion is collected by filtering with suction on a Büchner funnel, dried at 110°, and ground in a mortar to a fine black powder (Note 9). The yield is 130–140 g. (Notes 10 and 11).

2. Notes

1. The reactions involved in this preparation cannot be expressed quantitatively in a simple equation. The process has been investigated by Gröger.[1]

2. Barium nitrate is sparingly soluble in cold water and even less soluble in copper nitrate solution. It is therefore necessary to heat the mixture in order to bring both salts into solution together.

3. The warm, freshly prepared ammonium chromate solution may be used for the precipitation at once or may be allowed to cool to room temperature. However, the solution prepared as indicated is supersaturated at room temperature and deposits crystals on standing. If a stock solution of ammonium chromate is to be held over from day to day, a portion of the ammonia should be withheld and added immediately before precipitation. Chromic acid may be used for the preparation of the ammonium chromate solution provided the acid solution is kept cold while introducing a sufficient quantity of ammonia below the surface.

4. The amount of ammonia used is calculated to give a mother liquid that is neutral to litmus, allowance being made for the basic character of the precipitate. While a deviation either way affects the yield adversely, it is better not to try to adjust the end point after precipitation, but to make a slight correction on the amount of ammonia to be used for the next batch. The

mother liquor serves as its own indicator: if acid, the solution is yellow; if alkaline, a deep green.

5. A convenient-sized pan, 6 cm. deep, 19 cm. long, and 10 cm. wide, can be made from a sheet of nickel 1/32 inch thick.

6. The ignition of copper ammonium chromate causes a spontaneous exothermic reaction which proceeds with a rapid evolution of gas. Although the size of the charge ignited at one time is unimportant, the retaining vessels should not be too full, else there will be considerable mechanical loss of product. It is also inadvisable to break up the lumps of dried precipitate, as the lumpy condition diminishes spraying of the chromite on ignition.

7. The unextracted catalyst should be a bluish black, friable powder. It is a satisfactory catalyst for the dehydrogenation of alcohols and for the less difficult hydrogenation reactions, such as the reduction of nitro compounds. This mixture of copper chromite and copper oxide is somewhat less active and more susceptible of reduction to metallic copper than the catalyst from which the copper oxide has been removed by acid extraction.

8. If the washing is unduly prolonged, the catalyst tends to become colloidal and is difficult to separate either by decantation or filtration.

9. No special precautions are necessary in handling or storing the copper chromite catalyst, since it is unharmed by exposure to air or moisture.

10. Barium has been included as a catalyst component on account of its protective action against sulfate poisoning and its reported stabilization of the catalyst against reduction. Alternatively, the above procedure may be used for the preparation of a copper chromite catalyst containing no barium. In this case the barium nitrate is omitted and 242 g. (1 mole) of copper nitrate is used. All other details are the same as given above.

11. An alternative procedure described by Adkins[2] is as follows. Thirty-one grams of barium nitrate is dissolved in 820 cc. of distilled water which has been heated to 80°. To this hot solution is added 260 g. of copper nitrate trihydrate, and the

mixture is stirred and heated until solution is complete. Meanwhile, 151 g. of ammonium dichromate is dissolved in 600 cc. of distilled water and 225 cc. of 28 per cent aqueous ammonia added. The hot nitrate solution is poured in a thin stream with stirring into the ammonium chromate solution. The orange precipitate is collected on a filter, pressed, and sucked as dry as possible. It is dried in an oven at 75–80° for twelve hours, pulverized, and divided into three portions. Each portion is decomposed separately in a large porcelain casserole (15-cm. diameter) by heating over a free flame. The mass should be heated just hot enough to cause decomposition to take place at the minimum temperature. During the decomposition the powder is stirred continuously with a steel spatula, and the heating is regulated so that the evolution of gases does not become violent. This is accomplished by heating only one side of the casserole and by increasing the rate of stirring when the decomposition starts to spread throughout the mass. During this process the color of the powder changes from orange to brown and finally to black. When the entire mass has become black the evolution of gases ceases, and the powder is removed from the casserole and allowed to cool. The combined product is then stirred for thirty minutes with 600 cc. of 10 per cent acetic acid solution, collected on a filter, washed by suspending it six times in 100-cc. portions of water, dried for twelve hours at 125°, and pulverized. The yield of catalyst is 170 g.

3. Methods of Preparation

Copper chromite has been made by the ignition of basic copper chromate at a red heat and by the thermal decomposition of copper ammonium chromate.[1] The procedure given here is a modification of the latter method[3] in which barium ammonium chromate is also incorporated.[4] Copper-chromium oxide hydrogenation catalysts have also been prepared by grinding or heating together copper oxide and chromium oxides, by the decomposition of copper ammonium chromium carbonates or copper-chromium nitrates,[2,4] and by the low-temperature ignition of copper ammonium chromates.[5]

1 Gröger, Z. anorg. Chem. **58**, 412 (1908); **76**, 30 (1912).

2 Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," p. 12, University of Wisconsin Press, Madison, 1937.

3 Lazier, U. S. pats. 1,746,782 and 1,746,783 [C. A., **24**, 1649 (1930)]; U. S. pat. 1,964,000 [C. A. **28**, 5075 (1934)].

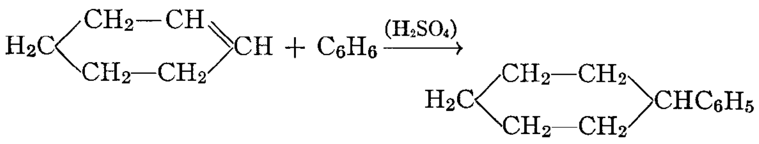
4 Connor, Folkers, and Adkins, J. Am. Chem. Soc. **53**, 2012 (1931); **54**, 1138 (1932).

5 Calingaert and Edgar, Ind. Eng. Chem. **26**, 878 (1934).

XIII

CYCLOHEXYLBENZENE

(Phenylcyclohexane)



Submitted by B. B. Corson and V. N. Ipatieff.
Checked by John R. Johnson and E. A. Cleveland.

1. Procedure

In a 1-l. three-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer are placed 468 g. (530 cc., 6 moles) of benzene and 92 g. (50 cc.) of concentrated sulfuric acid (sp. gr. 1.84). The mixture is cooled in an ice bath, and 164 g. (203 cc., 2 moles) of cyclohexene (Org. Syn. Coll. Vol. **I**, 177) is added with stirring over a period of one and one-half hours, while the temperature is maintained between 5° and 10°. Stirring is continued for an additional hour after all the cyclohexene has been added.

The hydrocarbon layer is separated, cooled in ice, and washed with four 50-cc. portions of cold concentrated sulfuric acid (Note 1). The material is then washed twice with warm water (50°), twice with 3 per cent sodium hydroxide solution, and twice with pure water (Note 2). The hydrocarbon mixture is dried over anhydrous calcium chloride (Note 3) and subjected twice to fractional distillation, using a 30-cm. Vigreux or similar column, and the cyclohexylbenzene is collected at 238–243° (uncorr.)/760 mm. (Notes 4 and 5). The yield is 210–220 g. (65–68 per cent of the theoretical amount).

2. Notes

1. The purpose of the sulfuric acid is to convert dicyclohexyl sulfate to cyclohexyl hydrogen sulfate, which is removed by the subsequent washing operations.

2. To avoid emulsification as much as possible it is advantageous to use warm water rather than cold, and dilute alkali rather than concentrated. The milkiness of the aqueous wash liquid represents only a very small loss of material.

3. It is well to allow suspended water to settle by standing overnight and separate again before adding the drying agent.

4. In a typical preparation the fractions collected during the second distillation were as follows: 78–85°, 296 g.; 85–235°, 2 g.; 235–238°, 2 g.; 238–243°, 215 g.; 243–265°, 2 g.; residue above 265°, 46 g.

5. The distillation residue becomes semi-solid on cooling owing to the separation of 1,4-dicyclohexylbenzene. The latter may be recovered by filtering with suction, washing with methyl alcohol, and crystallizing from acetone (using 4 cc. of acetone per gram of the crude solid). The yield of purified dicyclohexylbenzene, m.p. 100–101°, is 15–24 g.

3. Methods of Preparation

Cyclohexylbenzene has been prepared by the hydrogenation of biphenyl[1] and of cyclohexenylbenzene[2] over nickel, by the reaction of cyclohexyl chloride[3] or bromide[4] with benzene in the presence of aluminum chloride, and by the addition of benzene to cyclohexene in the presence of aluminum chloride,[5] sulfuric acid,[6] or boron halides.[7]

[1] Eijkman, Chem. Weekblad **1**, 7 (1903).
[2] Sabatier and Murat, Compt. rend. **154**, 1390 (1912).
[3] Kursanoff, Ann. **318**, 309 (1901).
[4] Braun, Ber. **60**, 1180 (1927).
[5] Bodroux, Ann. chim. (10) **11**, 511 (1929); Berry and Reid, J. Am. Chem. Soc. **49**, 3142 (1927); Corson and Ipatieff, ibid. **59**, 645 (1937).
[6] Deschauer, Ger. pat. 515,177 [Chem. Zentr. **1931**, **I**, 1829]; Truffault, Compt. rend. **202**, 1286 (1936); Corson and Ipatieff, J. Am. Chem. Soc. **59**, 645 (1937).
[7] Hofmann and Wulff, Brit. pat. 307,802 [Chem. Zentr. **1929**, **II**, 2101].

XIV

DICHLOROACETIC ACID

$$2CCl_3CH(OH)_2 + 2CaCO_3 \xrightarrow{(NaCN)} (CHCl_2CO_2)_2Ca + 2CO_2 + 2H_2O + CaCl_2$$

$$(CHCl_2CO_2)_2Ca + 2HCl \rightarrow CaCl_2 + 2CHCl_2CO_2H$$

Submitted by ARTHUR C. COPE, JOHN R. CLARK and RALPH CONNOR.
Checked by R. L. SHRINER and NEIL S. MOON.

1. Procedure

A SOLUTION of 250 g. (1.51 moles) of chloral hydrate (Note 1) in 450 cc. of warm water (50–60°) is placed in a 3-l. round-bottomed flask bearing a reflux condenser and thermometer (Note 2). The condenser is temporarily removed and 152.5 g. (1.52 moles) of precipitated calcium carbonate added; this is followed by 2 cc. of amyl alcohol (Note 3) and a solution of 10 g. of sodium cyanide (Note 4) in 25 cc. of water. Although the reaction is exothermic, the reaction mixture is heated with a low flame so that it reaches 75° in about ten minutes; at this point heating is discontinued. The temperature continues to rise to 80–85° during five to ten minutes and then drops. As soon as the temperature begins to fall the solution is heated to boiling and refluxed for twenty minutes. The mixture is then cooled to 0–5° in an ice bath, acidified with 215 cc. of concentrated hydrochloric acid (sp. gr. 1.18) and extracted with five 100-cc. portions of ether (Note 5). The combined ether extracts are dried with 20 g. of anhydrous sodium sulfate, the ether is removed by distillation from a steam bath, and the residue distilled in vacuum from a Claisen flask with a fractionating side

arm (Note 6). The yield of dichloroacetic acid, b.p. 99–104° at 23 mm., is 172–180 g. (88–92 per cent of the theoretical) (Note 7).

2. Notes

1. The chloral hydrate was of U.S.P. quality.

2. The amount of hydrogen cyanide evolved is small, and the reaction may be carried out in a hood without any special device for removing this gas. The use of mechanical stirring does not improve the results.

3. Amyl alcohol is added to decrease the amount of foaming.

4. The sodium cyanide was a technical grade.

5. The emulsion which often forms during the ether extraction may be broken by filtering through a fluted filter or with suction.

6. The product decomposes when distilled at atmospheric pressure.

7. The preparation has been carried out with equally good results using double the quantities given above.

3. Methods of Preparation

Dichloroacetic acid has been prepared by the chlorination of acetic [1] or chloroacetic [2] acid, by hydrolysis of pentachloroethane,[3] from trichloroacetic acid by electrolytic reduction [4] or the action of copper,[5] and by the action of alkali cyanides on chloral hydrate.[6] The method described here is essentially that of Delépine.[7]

[1] Müller, Ann. **133**, 159 (1865); U. S. pat. 1,921,717 (1933) [C. A. **27**, 5084 (1933)].
[2] Maumené, Compt. rend. **59**, 84 (1864).
[3] Fr. pat. 773,623 (1934) [C. A. **29**, 1437 (1935)].
[4] Brand, Ger. pat. 246,661 (1911) [C. A. **6**, 2496 (1912)].
[5] Doughty and Black, J. Am. Chem. Soc. **47**, 1091 (1925); Doughty and Derge, ibid., **53**, 1594 (1931).
[6] Wallach, Ann. **173**, 288 (1874); Pucher, J. Am. Chem. Soc. **42**, 2251 (1920); Chattaway and Irving, J. Chem. Soc. **1929**, 1038.
[7] Delépine, Bull. soc. chim. (4) **45**, 827 (1929).

XV

p-DINITROBENZENE

$$p\text{-}NO_2C_6H_4NH_2 + HNO_2 + HBF_4 \rightarrow p\text{-}NO_2C_6H_4N_2BF_4 + 2H_2O$$

$$p\text{-}NO_2C_6H_4N_2BF_4 + NaNO_2 \xrightarrow{(Cu)} p\text{-}C_6H_4(NO_2)_2 + N_2 + NaBF_4$$

Submitted by E. B. STARKEY.
Checked by LEE IRVIN SMITH and H. E. UNGNADE.

1. Procedure

THIRTY-FOUR GRAMS (0.25 mole) of *p*-nitroaniline is dissolved in 110 cc. of fluoboric acid solution (Note 1) in a 400-cc. beaker. The beaker is placed in an ice bath and the solution stirred with an efficient stirrer. A cold solution of 17 g. (0.25 mole) of sodium nitrite in 34 cc. of water is added dropwise. When the addition is complete, the mixture is stirred for a few minutes and filtered by suction on a sintered glass filter. The solid diazonium fluoborate is washed once with 25–30 cc. of cold fluoboric acid, twice with 95 per cent alcohol, and several times with ether (Note 2). The product weighs 56–59 g. (95–99 per cent of the theoretical amount).

Two hundred grams of sodium nitrite is dissolved in 400 cc. of water in a 2-l. beaker, and 40 g. of copper powder is added (Note 3). The mixture is stirred with an efficient stirrer (Note 4), and a suspension of the *p*-nitrophenyldiazonium fluoborate in 200 cc. of water is added slowly. Much frothing occurs, and 4–5 cc. of ether is added from time to time to break the foam. The reaction is complete when all the diazonium compound has been added. The product is filtered with suction, washed several times with water, twice with dilute sodium hydroxide solution, and again with water. The solid is dried in an oven at 110°, powdered, and extracted with 300-cc., 200-cc., and 150-cc.

portions of boiling benzene. The benzene is evaporated on a water bath, and the residue is crystallized from 120–150 cc. of boiling glacial acetic acid. The resulting reddish-yellow crystals, melting at 172–173°, weigh 28–34.5 g. (67–82 per cent yield) (Note 5). Recrystallization from alcohol yields pale yellow crystals melting at 173°.

2. Notes

1. Fluoboric acid is made by adding 184 g. of boric acid slowly, with constant stirring, to 450 g. of hydrofluoric acid (48–52 per cent) in a copper, lead, or silver-plated container placed in an ice bath.

2. A sintered glass filter should be used for filtering, and the fluoborate stirred well on the filter with each washing, before suction is applied. The diazonium fluoborate is stable and may be dried in a vacuum desiccator over phosphorus pentoxide.

3. The copper used was "Copper metal, precipitated powder."

4. In the decomposition reaction, efficient stirring is quite essential. An off-center stirrer is best suited for the purpose. The reaction should require about two hours. Less efficient stirring and a shorter reaction time cause the formation of an impure product which is not readily purified by crystallization.

5. *o*-Dinitrobenzene may be prepared from *o*-nitroaniline by the same general method. From 34 g. (0.25 mole) of the amine there is obtained 38 g. (63 per cent yield) of dry *o*-nitrobenzenediazonium fluoborate. After carrying out the reaction of the diazonium fluoborate with sodium nitrite and copper, the *o*-dinitrobenzene is separated by steam distillation instead of filtration and extraction. A little paraffin is added to diminish the troublesome foaming and creeping during distillation, and a special flask (Note 6) designed for such operations may be used advantageously. The crystalline product is filtered from the steam distillate and recrystallized from alcohol. The yield of *o*-dinitrobenzene, m.p. 116–116.5°, is 14–16 g. (33–38 per cent of the theoretical amount).

6. A Claisen flask modified as shown in Fig. 1 is used in the synthetic laboratories of the Eastman Kodak Company for the distillation of liquids which foam and creep badly. The large

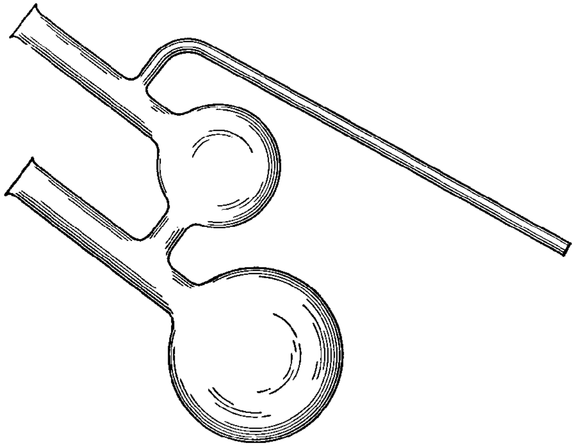


FIG. 1.

bulb inserted in the side arm should have a capacity about one-third that of the distillation flask. During distillation the flask is supported at the angle shown in the figure.

3. Methods of Preparation

p-Dinitrobenzene has been prepared from *p*-nitrosonitrobenzene by treatment with nitric acid;[1] from *p*-nitroaniline by the Sandmeyer reaction;[2] and by the oxidation of *p*-nitroaniline in concentrated sulfuric acid with ammonium persulfate.[3] *o*-Dinitrobenzene has been prepared in similar fashion from *o*-nitroaniline by the Sandmeyer reaction[4] and by oxidation with persulfate.[3] The preparation described above has been published recently.[5]

[1] Bamberger and Hübner, Ber. **36**, 3808 (1903).
[2] Meisenheimer and Patzig, ibid. **39**, 2526 (1906).
[3] Witt and Kopetschni, ibid. **45**, 1134 (1912).
[4] Körner and Contardi, Atti accad. Lincei (5) **23**, I, 283 (1914).
[5] Starkey, J. Am. Chem. Soc. **59**, 1479 (1937).

XVI

ETHYL BENZOYLDIMETHYLACETATE

(Ethyl α-Benzoyl-*iso*-butyrate)

$$(CH_3)_2CH—CO_2C_2H_5 + NaC(C_6H_5)_3 \rightarrow Na[(CH_3)_2CCO_2C_2H_5] + HC(C_6H_5)_3$$

$$C_6H_5COCl + Na[(CH_3)_2CCO_2C_2H_5] \rightarrow C_6H_5COC(CH_3)_2CO_2C_2H_5 + NaCl$$

Submitted by C. R. HAUSER and W. B. RENFREW, JR.
Checked by LEE IRVIN SMITH and E. C. BALLARD.

1. Procedure

To a freshly prepared solution of 0.187 mole of triphenylmethylsodium (p. 83), contained in the flask into which it was transferred after preparation, is added 21.7 g. (25 cc.; 0.187 mole) of pure ethyl *iso*-butyrate (Note 1). The mixture is shaken, and, after standing at room temperature for ten minutes, a solution of 26 g. (21.5 cc.; 0.186 mole) of pure benzoyl chloride in 50 cc. of dry ether is added, with shaking. The mixture becomes warm, and a white precipitate of sodium chloride separates immediately. After standing at room temperature for several hours the mixture is heated on a water bath and ether is distilled until the volume is reduced to 300–400 cc. A solution of 5 g. (5 cc.) of acetic acid in 300 cc. of water is added, and the mixture is shaken in a separatory funnel until two homogeneous layers separate on standing. The aqueous layer is drawn off and discarded; the ethereal layer is shaken with 10 per cent sodium carbonate solution and dried over calcium chloride or Drierite. The solution is filtered from the drying agent and distilled on a water bath until most of the ether is removed. The residue is cooled in a refrigerator, and the triphenylmethane which crystallizes is filtered with suction and washed with several small

portions of dry ether. The filtrate, after removal of ether, is distilled under reduced pressure and all material boiling up to 180° at 15 mm. collected. The distillate is redistilled and the fraction boiling up to 160° at 15 mm. is subjected to a final redistillation. There is obtained 20.5–22.5 g. (50–55 per cent of the theoretical amount) of ethyl benzoyldimethylacetate, b.p. 146–148° at 15 mm. or 133–135° at 9 mm. (Note 2).

2. Notes

1. It is essential to use pure reagents. Commercial ethyl isobutyrate may be purified satisfactorily by washing with 10 per cent sodium carbonate solution, drying over Drierite for several days, and fractionating through an effective column; material boiling over a one-degree range (110–111°) is recommended for this preparation. Benzoyl chloride was purified by distillation under reduced pressure, and a fraction collected over less than a two-degree range was used.

2. The submitters report that ethyl *iso*-butyryl-*iso*-butyrate (ethyl $\alpha,\alpha,\gamma,\gamma$-tetramethylacetoacetate) may be prepared in a similar manner, using *iso*-butyryl chloride instead of benzoyl chloride. The yield of this ester, b.p. 94.5–95.5° at 18 mm., is about 55 per cent of the theoretical.

3. Method of Preparation

The procedure described above is a modification of the method of Scheibler and Stein.[1]

[1] Scheibler and Stein, J. prakt. Chem. (2) **139**, 105 (1934).

XVII

ETHYL HYDROGEN SEBACATE

$$HO_2C—(CH_2)_8—CO_2H + C_2H_5OH \xrightarrow{(HCl)} C_2H_5O_2C—(CH_2)_8—CO_2H + H_2O$$

Submitted by Sherlock Swann, Jr., René Oehler, and R. J. Buswell.
Checked by Lee Irvin Smith and J. W. Clegg.

1. Procedure

In a 1-l. modified Claisen flask (Note 1), the side arm of which is corked, is placed a mixture of 202 g. (1 mole) of sebacic acid, 150 g. (0.58 mole) of diethyl sebacate (Note 2), 50 cc. of di-*n*-butyl ether (Note 3), and 30 g. (25 cc.) of concentrated hydrochloric acid (sp. gr. 1.19). A reflux condenser is connected to the top of the distilling flask.

The flask is heated in a Wood's metal bath at 160–170° until the mixture is completely homogeneous. The temperature of the bath is then lowered to 120–130°, and 60 cc. (1 mole) of 95 per cent ethyl alcohol is added to the solution through the condenser. The mixture is allowed to reflux for two hours. At the end of this period an additional 20-cc. portion of ethyl alcohol is poured into the solution and refluxing is continued for two hours longer.

The Wood's metal bath is allowed to cool to about 75° and the reaction mixture is subjected to distillation under reduced pressure, using a water pump (Note 4). The temperature of the bath is increased slowly and distillation is continued, with a water pump, until the bath reaches a temperature of about 125°. The bath is again cooled to 75–80° and the distillation is continued at lower pressure, using an oil pump.

The first fractions consist of a little alcohol, water, and di-*n*-butyl ether (Note 5). The next fraction is diethyl sebacate, b.p. 156–158° at 6 mm. (Note 6). Ethyl hydrogen sebacate is collected at 183–187° at 6 mm. The product melts at 34–36° and weighs 114–124 g. (50–54 per cent of the calculated amount, based on the sebacic acid used). Refractionation of the fore-run (b.p. 175–183°/6 mm.) and after-run (b.p. 187–195°/6 mm.) gives an additional 24–26 g. of pure monoester. The total yield is 138–150 g. (60–65 per cent of the theoretical amount) (Notes 7 and 8).

2. Notes

1. The column of the flask should be at least 35 cm. in length and well insulated. Wrapping the column with 10-mm. asbestos rope is satisfactory.

2. The addition of diester at the beginning of the reaction decreases its formation from the reactants so that the monoester becomes the main product.

Diethyl sebacate is prepared conveniently by refluxing 130 g. (0.65 mole) of sebacic acid with 250 g. of ethyl alcohol and 25 cc. of concentrated sulfuric acid. The yield is about 90 per cent, and the product boils at 156–158° at 6 mm.

3. Di-*n*-butyl ether is used in preference to other possible compounds because it permits the formation of a homogeneous reaction mixture.

4. At the beginning of the distillation the liquid in the flask foams excessively. It is advisable, therefore, to reduce the pressure gradually and not to use low pressures until the foaming subsides.

5. The di-*n*-butyl ether may be recovered in pure condition by a simple distillation after the water has been separated from it.

6. After the diethyl sebacate has distilled, it is well to drain the cooling water from the condenser in order to prevent the monoester from solidifying before reaching the receiver. The recovered diethyl sebacate weighs 150–175 g. and may be used directly in a subsequent preparation.

7. In subsequent runs the distillation residue is allowed to remain in the flask. In this way the yield is increased to 70–77 per cent for runs of one and two moles.

8. The submitters report that ethyl hydrogen adipate, b.p. 155–157° at 7 mm., has been prepared in 71–75 per cent yields on a one-mole scale by the same procedure.

3. Methods of Preparation

Ethyl hydrogen sebacate has been prepared by the direct esterification of sebacic acid with ethyl alcohol,[1] by the half-saponification of diethyl sebacate,[2] and by heating equimolecular quantities of sebacic acid and diethyl sebacate for several hours.[3]

[1] Neison, J. Chem. Soc. **29**, 319 (1876).
[2] Walker, ibid. **61**, 713 (1892); Brown and Walker, Ann. **261**, 125 (1891).
[3] Fourneau, Bull. soc. chim. (4) **43**, 859 (1928); (4) **45**, 834 (1929).

XVIII

HEXAMETHYLENE GLYCOL

(1,6-Hexanediol)

$$(CH_2)_4\left\langle\begin{matrix}CO_2C_2H_5\\ CO_2C_2H_5\end{matrix}\right. + 4H_2 \xrightarrow{(CuCr_2O_4)} (CH_2)_4\left\langle\begin{matrix}CH_2OH\\ CH_2OH\end{matrix}\right. + 2C_2H_5OH$$

Submitted by W. A. LAZIER, J. W. HILL, and W. J. AMEND.
Checked by R. L. SHRINER and J. F. KAPLAN.

1. Procedure

IN a steel reaction vessel (Note 1), capable of withstanding high pressures with an adequate safety factor (Note 2) and having a capacity of 400 cc. or more, are placed 252 g. (1.25 moles) of ethyl adipate (b.p. 144–145°/29 mm.) (Org. Syn. **17**, 32) and 20 g. of copper chromite catalyst, prepared either with or without the addition of barium (p. 31). The reaction vessel is closed, made gas tight, and secured in a suitable agitating device. After connection is made with the hydrogen supply, hydrogen is introduced until a pressure of 2000 to 3000 lb. per sq. in. is reached (Note 2).

Agitation is started, and the reaction system is heated as rapidly as possible to 255°. The temperature is maintained at 255° (Note 3), and hydrogenation is continued until hydrogen absorption is complete (Note 4). The agitation is now stopped, the vessel cooled, and the pressure released. With the aid of four 25-cc. portions of 95 per cent alcohol the contents is transferred to a 600-cc. beaker. The catalyst is removed by filtering or centrifuging, and is washed with four more 25-cc. portions of alcohol (Note 5). To the reaction product (Note 6), 50 cc. of 40 per cent sodium hydroxide solution is added, and the alcoholic

solution is boiled for two hours under a reflux condenser. The mixture is transferred to a 1-l. distilling flask and the alcohol removed by distilling to a vapor temperature of 95°. The hot residue is transferred to an apparatus for the continuous extraction of liquids (Org. Syn. **10**, 104), using 50 cc. of water to rinse the flask, and the solution is exhaustively extracted with ether (Note 7). The ether is distilled, and, after the removal of water and alcohol, the glycol is distilled under reduced pressure in a 250-cc. Claisen flask. The yield is 125–132 g. (85–90 per cent of the theoretical amount). Hexamethylene glycol boils at 143–144° (bath at 160°) under 4 mm. pressure and melts at 41–42°.

2. Notes

1. Suitable reaction vessels and apparatus for agitation of the reaction mixture are commercially available[1,2] or may be constructed.[3]

2. The pressure of hydrogen to be used is dependent upon the equipment available. Hydrogen in commercial cylinders is sold at a maximum pressure of 2000 lb. per sq. in. Special equipment for compressing hydrogen may be purchased at a reasonable price.[1] The original pressure of hydrogen should not be more than 2000 lb. if the maximum working pressure of the equipment for hydrogenation is 5000 lb. If the working pressure is 10,000 lb. the original pressure in the reaction vessel may be as much as 3000 lb. The full operating pressure is not applied in the beginning since the pressure will rise as the reaction vessel is heated; thus, at 255° the pressure will be 1.8 times as high as it was at 20°. The pressure drops as hydrogenation proceeds; the progress of the reaction may be followed by the change in pressure readings, and completion of the reaction is indicated by the constancy of the pressure readings.

3. The temperature is controlled preferably by an automatic controller operating through a relay which cuts off periodically the supply of electric current.

4. The time (six to twelve hours) required to complete the reaction is a function of the pressure of the hydrogen, activity of the catalyst, and purity of the ethyl adipate. Unless a high pressure of hydrogen is used originally or the reaction vessel is of large capacity (2 l.) it will be necessary to introduce more hydrogen into the reaction vessel so that the pressure is never less than 1500 lb. per sq. in. if the reaction is to run smoothly to completion.

5. The catalyst is most readily removed by centrifuging. If this is not convenient, it may be collected on a sintered glass filter or Büchner funnel.

6. At this point, the amount of unchanged ester present may be determined by obtaining the saponification value of the weighed mixture. This procedure is especially desirable when the condition of the apparatus with respect to the possible presence of poisons is unknown, or a new preparation of catalyst is being used.

After a batch of catalyst has been tested and the apparatus calibrated so that complete reduction is assured, it is possible to isolate the glycol by fractional distillation at this stage.

7. The time required for complete extraction varies from twenty-four to fifty hours. It depends on the design of the apparatus and the rate of distillation of the ether. The extraction can be followed by observing the decrease in volume of the aqueous layer containing the glycol. The extraction is complete when the evaporation of a small amount of the supernatant ether on a watch glass leaves no residue. Benzene may be substituted for ether in the extraction step.

3. Methods of Preparation

Hexamethylene glycol has been prepared by treating hexamethylene iodide with silver acetate and hydrolyzing the acetate,[4] by hydrolyzing the bromide,[5] by reducing ethyl adipate with sodium and alcohol,[6] and by the method here described.[7] The catalytic hydrogenation over copper-chromium oxide of the

carbethoxy group to the carbinol group is a very useful and general method for the preparation of mono- and dihydric alcohols.[3,8]

1 American Instrument Company, Silver Springs, Maryland.

2 Parr Instrument Company, Moline, Illinois.

3 Adkins, Ind. Eng. Chem. Anal. Ed. **4**, 342 (1932); "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," pp. 29–39, University of Wisconsin Press, Madison, Wisconsin, 1937.

4 Hamonet, Bull. soc. chim. (3) **33**, 533 (1905).

5 Haworth and Perkin, J. Chem. Soc. **65**, 591 (1894).

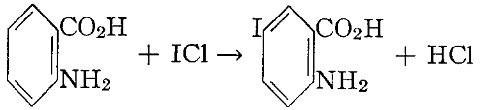
6 Bouveault and Blanc, Compt. rend. **137**, 328 (1903); Bull. soc. chim. (3) **31**, 1203 (1904).

7 Lazier, U. S. pat. 2,079,414 [C. A. **31**, 4340 (1937)]; U. S. pat. 2,137,407 (1938).

8 Adkins and Folkers, J. Am. Chem. Soc. **53**, 1095 (1931); **54**, 1145 (1932); Wojcik and Adkins, ibid. **55**, 4939 (1933).

XIX

5-IODOANTHRANILIC ACID



Submitted by V. H. WALLINGFORD and PAUL A. KRUEGER.
Checked by F. C. WHITMORE and L. H. SUTHERLAND.

1. Procedure

IN a 3-l. beaker, 110 g. (0.8 mole) of anthranilic acid (Note 1) is dissolved in 1 l. of water and 80 cc. of C.P. concentrated hydrochloric acid (sp. gr. 1.19), and the solution is cooled to 20°. In a 2-l. beaker a solution of iodine monochloride in hydrochloric acid is prepared by diluting 140 cc. of C.P. concentrated hydrochloric acid with 500 cc. of cold water, adding just sufficient crushed ice to bring the temperature to 5°, and, during about two minutes, stirring in 131 g. (0.8 mole) of iodine monochloride (Org. Syn. **12**, 29).

The iodine monochloride solution at 5° is stirred rapidly into the anthranilic acid solution at 20°. 5-Iodoanthranilic acid separates almost immediately as a granular, tan to violet precipitate, and the reaction temperature rises to 18–22°. The mixture is stirred for an hour, while warming to room temperature, then filtered on a 13-cm. Büchner funnel. The acid is pressed as dry as possible, washed with three 100-cc. portions of cold water, and then dried at 90–100°. There is obtained 185–189 g. (88–90 per cent yield) of brown to purple acid which melts at 185–190°, with decomposition (Note 2).

5-Iodoanthranilic acid is best purified by recrystallization of its ammonium salt, as follows: To 100 g. of the acid in a 400-cc. beaker is added 200 cc. of hot water, and the acid is dissolved by stirring in concentrated ammonia (sp. gr. 0.9) until solution is

complete at 60° and there is a slight excess of ammonia. About 40 cc. of concentrated ammonia is required. Sodium hydrosulfite is added in about 1-g. portions until no further bleaching action is observed, about 5 g. of decolorizing charcoal is added, and after stirring three minutes the mixture is filtered with suction on a preheated Büchner funnel into a preheated flask. The filter is washed with 10 cc. of boiling water.

The combined filtrate and washings are transferred to a 400-cc. beaker, allowed to cool slowly without agitation until crystal formation appears complete, then cooled to 5°. The crystalline ammonium salt is then removed by suction filtration on a large Büchner funnel, washed with 15 cc. of ice water, sucked as dry as possible, and spread in a thin layer on an enameled or glass tray and allowed to dry in air at 35–50°. The yield of yellow to violet ammonium salt is 80–89 g., representing a recovery of 76–84 per cent (Notes 3 and 4).

The ammonium salt is dissolved in three parts of hot water, ammonia is added if necessary to effect complete solution at 60°, the solution is again treated with sodium hydrosulfite and 3–4 g. of decolorizing charcoal, filtered hot, and the 5-iodoanthranilic acid is precipitated by adding C.P. hydrochloric acid in 3- to 5-cc. portions, stirring thoroughly after each addition, until the reaction mixture is just faintly acid to Congo red. Ice is then added until the temperature is reduced to 20°, and the precipitated acid is removed by suction filtration, washed freely with cold water, and dried at 100–110° (Note 5). 5-Iodoanthranilic acid is almost quantitatively precipitated from its ammonium salt solution and is obtained as a yellow powder, m.p. 190–195° (decomp.) (Note 6).

2. Notes

1. Commercial "Acid Anthranilic Sublimed" is satisfactory.

2. The decomposition point varies with the method of determination. The values given herein were determined by placing the sample in a capillary tube, inserting the tube in the bath at a temperature 25° below the decomposition point, and heating at the rate of 2–3° per minute.

3. The ammonium salt is not stable under the drying conditions. The dry product is a mixture of 5-iodoanthranilic acid and its ammonium salt. Contact with air may change its color from yellow to violet.

4. Crude 5-iodoanthranilic acid is recovered from the mother liquor by carefully making it just acid to Congo red, using a spot plate, with concentrated hydrochloric acid, cooling to 20°, filtering, washing freely with cold water, and drying at 90–110°. This acid can be added to crude acid in further crystallizations or worked up alone.

5. The drying oven must be one with good air circulation and uniform temperature control; drying at 120° causes the evolution of considerable amounts of free iodine.

6. This product is sufficiently pure for conversion to *m*-iodobenzoic acid (p. 57). If greater purity is desired the ammonium salt can be recrystallized from twice its weight of water, between 45° and 5°, with 85–90 per cent recovery. When the salt remains nearly white after drying, the acid precipitated from it melts with decomposition at a temperature above 210°. Four or five recrystallizations may be required.

3. Methods of Preparation

5-Iodoanthranilic acid has been prepared by the reduction of 2-nitro-5-iodobenzoic acid,[1] by treatment of anthranilic acid with iodine in potassium hydroxide solution,[2] by treatment of the anhydride of 5-hydroxymercurianthranilic acid with iodine in aqueous potassium iodide solution,[3] and by iodination of anthranilic acid in glacial acetic acid solution with iodine monochloride.[4]

[1] Grothe, J. prakt. Chem. (2) **18**, 326 (1878).
[2] Wheeler and Johns, Am. Chem. J. **43**, 403 (1910).
[3] Schoeller and Hueter, Ber. **47**, 1938 (1914).
[4] Borsche, Weussmann, and Fritzsche, ibid. **57**, 1774 (1924).

XX

IODOBENZENE

$$C_6H_5NH_2 + NaNO_2 + 2HCl \rightarrow C_6H_5N_2Cl + 2H_2O + NaCl$$
$$C_6H_5N_2Cl + KI \rightarrow C_6H_5I + N_2 + KCl$$

Submitted by H. J. Lucas and E. R. Kennedy.
Checked by John R. Johnson and P. L. Barrick.

1. Procedure

In a 3- or 5-gallon stoneware crock are placed 950 cc. (1130 g., 11.7 moles) of concentrated hydrochloric acid (sp. gr. 1.19), 950 cc. of water, 200 g. (196 cc., 2.15 moles) of aniline, and 2 kg. of ice (Note 1). The mixture is agitated by a mechanical stirrer, and, as soon as the temperature drops below 5°, a chilled solution of 156 g. (2.26 moles) of sodium nitrite in a measured volume (700–1000 cc.) of water is introduced fairly rapidly from a separatory funnel, the stem of which projects below the surface of the reaction mixture. The addition should not be fast enough to cause the temperature to rise to 10° or to cause evolution of oxides of nitrogen. The last 5 per cent of the nitrite solution is added more slowly, and the reaction mixture is tested with starch-iodide paper at intervals until an excess of nitrous acid is indicated.

Stirring is continued for ten minutes, and if necessary the solution is filtered rapidly through a loose cotton plug in a large funnel. An aqueous solution of 358 g. (2.16 moles) of potassium iodide is added and the reaction mixture allowed to stand overnight. The mixture is transferred to a large flask (or two smaller flasks) and heated on a steam bath, using an air-cooled reflux condenser, until no more gas is evolved, then allowed to cool and stand undisturbed until the heavy organic layer has settled thoroughly. A large part of the upper aqueous layer is siphoned off, and discarded (Note 2). The residual aqueous and organic

layers are made alkaline by the cautious addition of strong sodium hydroxide solution (100–125 g. of solid technical sodium hydroxide is usually required) and steam-distilled at once. The last one-third of the steam distillate is collected separately and combined with the aqueous layer separated from the earlier portions of the distillate. This mixture is acidified with 5–10 cc. of concentrated sulfuric acid and steam-distilled again. The iodobenzene from this operation is combined with the main portion and dried with 10–15 g. of calcium chloride (Notes 3 and 4). Distillation under reduced pressure gives 327–335 g. (74–76 per cent of the theoretical yield) of iodobenzene, b.p. 77–78°/20 mm. or 63–64°/8 mm. (Note 5).

2. Notes

1. If more ice is used a portion remains unmelted after the diazotization is completed.

2. If a good separation has been made not more than 1–2 g. of iodobenzene is lost with the upper layer.

3. An appreciable amount of iodobenzene is retained by the solid calcium chloride. By treating the spent drying agent with water 8–12 g. of iodobenzene can be recovered.

4. The crude iodobenzene weighs 350–355 g. (80 per cent of the theoretical yield) and is pure enough for many purposes without redistillation.

5. Care should be taken not to push the distillation too far, towards the end, or a colored distillate will be obtained.

3. Methods of Preparation

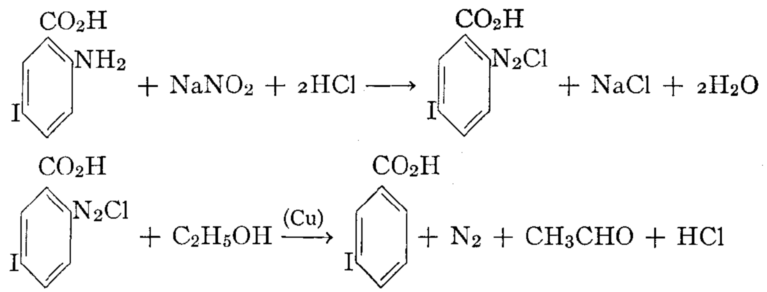
The preparation of iodobenzene by iodination of benzene, with iodine and nitric acid, and a survey of preparative methods have been given in an earlier volume.[1] The present procedure, based upon the method of Gattermann,[2] gives a purer product.

[1] Org. Syn. Coll. Vol. I, 316 (1932).

[2] Gattermann-Wieland, "Laboratory Methods of Organic Chemistry," p. 283. Translated from the twenty-fourth German edition by W. McCartney, The Macmillan Company, New York, 1937.

XXI

m-IODOBENZOIC ACID



Submitted by V. H. Wallingford and Paul A. Krueger.
Checked by F. C. Whitmore and L. H. Sutherland.

1. Procedure

In a 1-l. flask 132 g. (0.5 mole) of 5-iodoanthranilic acid (p. 52) and 35 g. (0.5 mole) of sodium nitrite are dissolved in a mixture of 500 cc. of warm water and 60 cc. of 30 per cent sodium hydroxide solution. After cooling to 20° the solution is added from a dropping funnel, over a period of fifteen to twenty minutes, to a well-stirred mixture of 250 cc. of concentrated hydrochloric acid (sp. gr. 1.18) and 250 g. of ice in a 2-l. beaker; more ice is added, as required, to keep the temperature below 20°. The insoluble, yellow diazonium compound separates before completion of the diazotization. After all the solution has been added from the dropping funnel, the reaction mixture is stirred for five minutes and tested for excess nitrous acid with starch-iodide paper. If required, small amounts of solid sodium nitrite are added and the test is repeated at three-minute intervals until a slight excess is definitely established. The diazonium compound is allowed to settle and as much as possible of the

supernatant liquor is decanted, leaving a slurry of diazonium compound.

In a 3-l. beaker are placed 750 cc. of 95 per cent ethyl alcohol and 1.5 g. of finely ground copper sulfate, and the mixture is heated on a hot plate or steam bath to 70°. The diazonium slurry is added in about 30-cc. portions to the well-stirred alcohol; the temperature is kept between 60° and 70°, and the nitrogen evolution is allowed to subside considerably between additions. The final traces of diazonium slurry are washed into the alcohol with small amounts of the decanted solution, the remainder of which is then added to the alcohol in 100-cc. portions. The reaction mixture is heated and stirred at 65–70° for half an hour, and then cooled without agitation to 5°. The *m*-iodobenzoic acid which separates is filtered with suction on a Büchner funnel, washed with three 50-cc. portions of cold water, and dried at 90–110°. There is obtained 107–116 g. of crude, brown *m*-iodobenzoic acid (86–93 per cent of the theoretical amount) (Note 1).

The crude *m*-iodobenzoic acid is purified by recrystallization of its ammonium salt. To 100 g. of the acid in a 250-cc. beaker is added 75 cc. of hot water, and the acid is partially neutralized with 24 cc. of concentrated ammonia (sp. gr. 0.9). After stirring at 80° until no more acid dissolves, neutralization is completed by adding 2–5 cc. of ammonia, until the acid is completely dissolved. The solution is heated to 90°, 1 g. of decolorizing charcoal is added, and the mixture is filtered with suction using a preheated Büchner funnel and filter flask. The residue on the filter is washed with 15 cc. of boiling water. The combined washings and filtrate are transferred to a 250-cc. beaker and allowed to cool without agitation to 25–35°, then cooled by any convenient means to 5°. The ammonium *m*-iodobenzoate crystals are filtered and pressed as dry as possible on a Büchner funnel, spread in a thin layer on a glass or enameled tray, and dried at a temperature not above 60°. There is obtained 86–90 g. of faintly yellow to tan prisms of the ammonium salt, a recovery of 76–81 per cent (Note 2).

The ammonium salt thus obtained is recrystallized until white by dissolving it in an equal weight of water at 80° and cooling to 5°. The recovery in this purification averages 75–85 per cent (Note 3).

m-Iodobenzoic acid melting at 187–188° is obtained by dissolving pure ammonium *m*-iodobenzoate in four times its weight of hot water, precipitating the acid by acidifying the solution to Congo red with concentrated hydrochloric acid, adding ice to reduce the temperature to 20°, filtering by suction, washing the acid freely with cold water, and drying at 90–110° (Note 4).

2. Notes

1. Evaporation of the mother liquors to incipient turbidity and cooling the concentrate to 5° will produce a few grams of acid, but this is usually very impure and tarry.

2. Ammonium *m*-iodobenzoate is not stable under these drying conditions. The product at this point contains some free acid.

3. In some runs as many as five recrystallizations failed to furnish white crystals of the ammonium salt, but, in these runs, precipitation of the acid after three or four crystallizations gave a product having the correct melting point.

Mother liquors from the crystallization are best worked up by acidifying to Congo red with concentrated hydrochloric acid, filtering, washing, drying, and reworking the recovered acid.

4. The total overall yield of pure acid form the crude depends on the amount of crude acid taken, the care exercised to avoid material losses, and the number of recrystallizations required to attain the desired purity. Without recoveries from mother liquors, 100 g. of crude acid, after conversion to the ammonium salt, and three recrystallizations of the latter, gave 40–45 g. of pure acid. Overall recovery of pure acid from 100 g. of the crude gave 50 g. of pure acid melting at 187–188°, 10 g. of less pure acid melting at 184–186°, and about 10 g. of a tarry solid residue.

3. Methods of Preparation

m-Iodobenzoic acid has been prepared by diazotization of *m*-aminobenzoic acid and treatment with potassium iodide in acid solution,[1,2,3] and by the action of concentrated nitric acid on a glacial acetic acid solution of iodine and benzoic acid.[4]

[1] Griess, Ann. **113**, 336 (1860).
[2] Cohen and Raper, J. Chem. Soc. **85**, 1273 (1904).
[3] Cattelain, Bull. soc. chim. (4) **41**, 1546 (1927).
[4] Datta and Chatterjee, J. Am. Chem. Soc. **41**, 294 (1919).

XXII

dl-LYSINE HYDROCHLORIDES

$$C_6H_5CONH(CH_2)_4\underset{\displaystyle Br}{CH}CO_2H \xrightarrow{NH_3} C_6H_5CONH(CH_2)_4\underset{\displaystyle NH_2}{CH}CO_2H$$

$$\xrightarrow{H_2O + HCl} ClNH_3(CH_2)_4\underset{\displaystyle NH_3Cl}{CH}CO_2H \xrightarrow{Pyridine} ClNH_3(CH_2)_4\underset{\displaystyle NH_2}{CH}CO_2H$$

Submitted by J. C. Eck and C. S. Marvel.
Checked by C. R. Noller and William Munich.

1. Procedure

(*A*) *dl-ε-Benzoyllysine.*—A solution of 180 g. (0.57 mole) of ε-benzoylamino-α-bromocaproic acid (p. 18) in 2 l. of aqueous ammonia (sp. gr. 0.9) is filtered into a 5-l. flask and allowed to stand for two days. The crystals formed at the end of this time are filtered (Note 1) and the filtrate evaporated on a steam bath at reduced pressure to about 1 l. The crystals are filtered, combined with the first crop, and washed with 100 cc. of alcohol and finally with 100 cc. of ether. The aqueous filtrate is evaporated under reduced pressure to dryness and the residue washed with two 100-cc. portions of water to remove the ammonium bromide, and then with 50 cc. of alcohol followed by 50 cc. of ether. The total yield of ε-benzoyllysine, melting at 265–270°, is 100–116 g. (70–81 per cent of the calculated amount).

(*B*) *dl-Lysine Dihydrochloride.*—A solution of 100 g. (0.4 mole) of benzoyllysine in a mixture of 600 cc. of hydrochloric acid (sp. gr. 1.18) and 400 cc. of water is boiled under a reflux condenser for ten hours. The mixture is cooled and the benzoic acid removed by filtration. The filtrate is evaporated on a

water bath under reduced pressure until a thick syrup remains. The syrup is transferred to a 1.5-l. beaker by means of four volumes (about 400 cc.) of hot absolute alcohol and filtered if necessary. The solution is cooled to 15–20°, and 500 cc. of ether is added slowly with stirring. The precipitate, after filtering and drying, melts at 187–189° and weighs 67–75 g. (76–85 per cent of the calculated amount); it is analytically pure lysine dihydrochloride (Note 2).

(*C*) *dl-Lysine Monohydrochloride.*—To a solution of 55 g. (0.25 mole) of lysine dihydrochloride in 1 l. of boiling 95 per cent alcohol (Note 3) is added, with stirring, a solution of 25 g. (0.32 mole) of pyridine in 40 cc. of hot 95 per cent alcohol. The white, crystalline monohydrochloride separates immediately. After cooling overnight in a refrigerator the solid is filtered and washed with two 50-cc. portions of cold absolute alcohol. After drying, the product melts at 260–263° and weighs 42–43 g. (91–94 per cent of the calculated amount).

For further purification to remove any pyridine hydrochloride, the above product is dissolved in 85 cc. of boiling water, and 650 cc. of boiling 95 per cent alcohol added with stirring. After cooling overnight in the refrigerator the solid is filtered, and washed with one 20-cc. portion of cold absolute alcohol. There is obtained 40–42 g. (95–97 per cent recovery) of monohydrochloride melting at 263–264° (corr.).

2. Notes

1. If no crystallization has taken place, one proceeds directly with the concentration.

2. If a product of lower melting point is obtained, it may be purified by dissolving in 1 l. of hot 95 per cent alcohol, filtering if necessary, cooling, and without removing any material that may have crystallized out, adding slowly with stirring 1500 cc. of ether. If the product separates as an oil it will soon crystallize on standing. The checkers found that one lot of 75 g. melting at 173–178° when treated in this way gave 67 g. (89 per cent recovery) melting at 187–189°.

3. If a clear solution is not obtained the hot solution should be filtered before the addition of pyridine.

3. Method of Preparation

The above procedure for *dl*-ε-benzoyllysine and *dl*-lysine hydrochloride is a modification [1] of that published by Braun.[2]

[1] Eck and Marvel, J. Biol. Chem. **106**, 387 (1934).

[2] Braun, Ber. **42**, 844 (1909).

XXIII

METHYL NITRATE

$$CH_3OH + HONO_2 \xrightarrow{(H_2SO_4)} CH_3ONO_2 + H_2O$$

Submitted by Alvin P. Black and Frank H. Babers.
Checked by John R. Johnson and H. B. Stevenson.

1. Procedure

In a flask cooled in an ice bath, are mixed 425 g. (300 cc.; 4.6 moles) of c.p. nitrous-free, concentrated nitric acid (sp. gr. 1.42) (Note 1) and 550 g. (300 cc.) of c.p. concentrated sulfuric acid (sp. gr. 1.84). In a second flask, also cooled in an ice bath, 92 g. (50 cc.) of c.p. concentrated sulfuric acid is added to 119 g. (150 cc.; 3.7 moles) of pure methyl alcohol (Note 2) while the temperature is maintained below 10°.

One-third of the cold nitric-sulfuric mixture is placed in each of three 500-cc. Erlenmeyer flasks (Note 3), and each portion is treated separately with one-third of the methyl alcohol-sulfuric acid mixture, with constant shaking and thorough mixing (Note 4). The temperature is allowed to rise fairly rapidly to 40° and kept at this point by external cooling. During the addition of the methyl alcohol-sulfuric acid, most of the ester separates as an almost colorless oily layer above the acid. The time required for completion of the reaction is two to three minutes for each flask. The reaction mixtures are allowed to stand in the cold for an additional fifteen minutes but not longer. The lower layer of spent acid is separated promptly and poured at once into a large volume of cold water (about 1 l. for each portion) to avoid decomposition which quickly ensues with copious evolution of nitrous fumes.

The combined ester layers are washed with two 25-cc. portions of ice-cold salt solution (sp. gr. 1.17) (Note 5). A small quantity (8–10 drops) of concentrated sodium hydroxide solution is added to the second wash liquid until it has a faintly alkaline reaction to litmus. The ester is washed free of alkali with ice-cold salt solution and finally washed with two 15-cc. portions of ice water (Note 6). The product is treated with 10–15 g. of anhydrous calcium chloride and allowed to stand with occasional shaking for an hour at 0°. It is then decanted onto a fresh 5-g. portion of the drying agent and after standing for one-half hour is filtered. The crude ester without further purification (Note 7) may be used directly for most synthetic purposes, such as the preparation of phenylnitromethane (p. 73). The yield is 190–230 g. (66–80 per cent of the theoretical amount). *The crude ester should be used promptly and not stored.*

2. Notes

1. Colored specimens of nitric acid may be treated with a small quantity of urea (about 1–2 g. per 100 cc.), but this is unnecessary unless the acid is appreciably colored.

2. Commercial synthetic methanol of high grade was used without further purification. This material is believed to be superior to wood alcohol for this preparation.

3. It should be noted that volume contractions occur in mixing the reagents. The total volume of the mixed acids is about 585 cc. (instead of 600 cc.), and that of the methyl alcohol-sulfuric acid is about 182 cc. (instead of 200 cc.).

4. The treatment of methanol with a mixture of concentrated nitric and sulfuric acids is not without elements of danger, and *adequate precautionary measures should be taken.* However, the submitters report that more than one hundred preparations were carried out without a single explosion or violent decomposition.

5. This corresponds to a 22 per cent solution of sodium chloride. This particular solution was found to give satisfactory separations and obviate emulsions.

6. Traces of acid remaining in the ester facilitate decomposition, and violent explosions may occur if such specimens are heated.

7. Methyl nitrate may be distilled if adequate precautions are taken. The ester must not be heated suddenly, and must not contain any free acid. *Distillation is not recommended*, as the crude ester (after washing and drying) gives as good yields as the distilled product in most synthetic reactions. The loss in distillation is small, and the pure material distils at 64.5–65°. Care must be taken to avoid superheating the residue in the distilling flask.

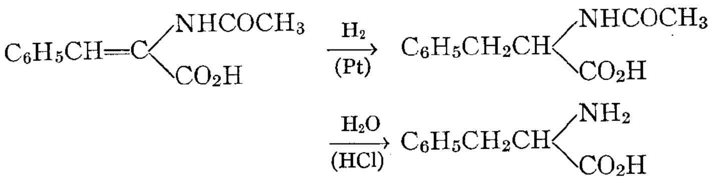
3. Methods of Preparation

Methyl nitrate has been prepared by distilling a methyl alcohol-nitric acid mixture to which methyl alcohol-sulfuric acid is added dropwise,[1] and by the use of dilute nitric acid in a procedure similar to that given above.[2] Neither of these methods is satisfactory, and explosions occur frequently.

[1] Lea, Chem. Zentr. **1862**, 602.
[2] Delépine, Bull. soc. chim. (3) **13**, 1044 (1895).

XXIV

dl-β-PHENYLALANINE



Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

A solution of 20.5 g. (0.1 mole) of α-acetaminocinnamic acid (p. 1) in 150 cc. of glacial acetic acid (Note 1) is placed in the bottle of a Burgess-Parr reduction apparatus, 0.5 g. of platinum oxide catalyst (Org. Syn. Coll. Vol. **I**, 452; **17**, 98) is added, and the mixture shaken in an atmosphere of hydrogen under an initial pressure of 40 lb. per sq. in. until the calculated amount of gas is taken up; usually about two hours is required (Notes 2 and 3). When the reduction is complete, the catalyst is removed by suction filtration and washed with a little water. The combined filtrate and washings are evaporated to dryness under diminished pressure on a water bath.

The crystalline residue (Note 4) is taken up in 400 cc. of 1 *N* hydrochloric acid, transferred to a 1-l. flask fitted with a reflux condenser, and boiled for ten hours (Note 5). The resulting solution is evaporated to dryness under diminished pressure on the water bath; to the residue 100 cc. of water is added slowly through a dropping funnel at about the same rate as that at which it distils, in order to remove the excess hydrochloric acid as completely as possible. The residue is then taken up in 30–40

cc. of boiling water, and the pH of the solution adjusted until it is basic to Congo red, but still acid to litmus, by careful addition of concentrated ammonia and acetic acid (Note 6). At this point two volumes of 95 per cent alcohol is added to aid in the separation of the phenylalanine. The mixture is placed in the refrigerator for a day, after which the product is transferred to a Büchner funnel, and washed first with three 25-cc. portions of ice-cold water and then with alcohol. The yield is 14.5 g. The filtrate is evaporated to dryness under reduced pressure on the water bath, and the residue is extracted with about 70 cc. of ice-cold water in three or four portions. The insoluble material, after washing with 95 per cent alcohol, is added to the main fraction of phenylalanine. The total yield is 16 g. (Note 7).

The combined fractions weighing about 16 g. are dissolved in a minimum amount of boiling water (Note 8), two volumes of 95 per cent alcohol is added, and the flask is placed in a refrigerator overnight to complete crystallization. The phenylalanine is transferred to a Büchner funnel, washed with several small portions of ice-cold water, and finally with alcohol. The yield is 10.5–11 g. By concentrating the filtrate and washings further, 3–3.5 g. of product can be obtained conveniently. The total yield is 14–14.3 g. (85–86 per cent of the theoretical amount) of analytically pure phenylalanine.

2. Notes

1. It may be necessary to warm the mixture in order to dissolve the acetaminocinnamic acid completely in this amount of acetic acid. In this case the solution should be allowed to cool to room temperature before it is placed in the reduction apparatus.

2. When the calculated amount of hydrogen is taken up, the catalyst is no longer colloidal and the rate of hydrogen uptake becomes very slow.

3. With freshly prepared and moist catalyst the benzene ring may also be reduced, in which case N-acetylhexahydrophenylalanine is formed. When this occurs, the hydrogen uptake continues at a rapid rate even after the amount required for hydrogenation of the side chain has been taken up. After recrystallization from water or dilute alcohol, the hexahydro compound forms needles melting at 178°.

4. Pure N-acetylphenylalanine can be obtained at this point by recrystallizing the residue from hot water or from hot dilute alcohol; it forms colorless needles melting at 150–151°.

5. Hydrolysis with 1 N hydrochloric acid is not complete if less than ten hours is allowed. With higher acid concentrations the hydrolysis can be completed more rapidly.

6. When the solution is made just basic to Congo red, the product separates in an almost solid mass; addition of alcohol at this point facilitates the testing of the pH by disintegrating the mass and decreases the solubility of the product.

7. The product at this point contains about 2.5 per cent of ammonium chloride; allowing for this the yield of phenylalanine is 94 per cent. Unless absolutely pure phenylalanine is required, the subsequent recrystallization can be omitted.

8. Phenylalanine dissolves rather slowly in boiling water. It is therefore convenient to start with an excess of water and to concentrate the solution over a free flame until crystals begin to separate from the hot solution.

3. Methods of Preparation

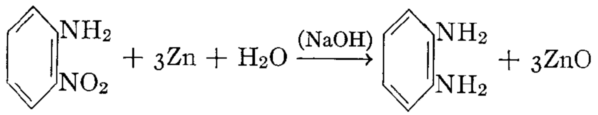
To the methods of preparation cited by Gillespie and Snyder[1] the following may be added: the reduction of phenylpyruvic acid in alcoholic-ammoniacal solution with hydrogen in the presence of platinum catalyst;[2] and the reduction of α-acetaminocinnamic acid with hydrogen in the presence of platinum followed by hydrolysis of the resulting acetylphenylalanine.[3]

[1] Gillespie and Snyder, Org. Syn. **14**, 80 (1934).
[2] Knoop and Oesterlin, Z. physiol. Chem. **148**, 311 (1925).
[3] Bergmann, Stern, and Witte, Ann. **449**, 280 (footnote) (1926).

XXV

o-PHENYLENEDIAMINE

(1,2-Diaminobenzene)



Submitted by E. L. Martin.
Checked by W. W. Hartman and S. S. Fierke.

1. Procedure

In a 1-l. three-necked, round-bottomed flask fitted with a liquid-sealed mechanical stirrer and reflux condenser, are placed 69 g. (0.5 mole) of *o*-nitroaniline, 40 cc. of a 20 per cent solution of sodium hydroxide, and 200 cc. of 95 per cent ethanol. The mixture is stirred vigorously and heated on a steam bath until the solution boils gently. The steam is turned off and 10-g. portions of 130 g. (2 gram atoms) of zinc dust (Note 1) are added, frequently enough to keep the solution boiling (Notes 2, 3). After the addition of the zinc dust has been completed the mixture is refluxed with continued stirring for one hour; the color of the solution changes from a deep red to nearly colorless. The hot mixture is filtered by suction, and the zinc residue is returned to the flask and extracted with two 150-cc. portions of hot alcohol. To the combined filtrates is added 2–3 g. of sodium hydrosulfite, and the solution is concentrated under reduced pressure (using a water pump), on a steam bath, to a volume of 125–150 cc. After cooling thoroughly in an ice-salt bath, the faintly yellow crystals are collected, washed once with a small amount of ice water, and dried in a vacuum desiccator. The yield of crude *o*-phenylenedi-

amine melting at 97–100° is 46–50 g. (85–93 per cent of the theoretical amount). If a purer product is desired, the material is dissolved in 150–175 cc. of hot water containing 1–2 g. of sodium hydrosulfite and treated with decolorizing charcoal. After cooling thoroughly in an ice-salt mixture, the colorless crystals are filtered by suction and washed with 10–15 cc. of ice water. The purified *o*-phenylenediamine weighs 40–46 g. (74–85 per cent of the theoretical amount) and melts at 99–101° (Notes 4 and 5).

2. Notes

1. The zinc dust should be at least 80 per cent pure, and the amount used should be equivalent to 130 g. of 100 per cent material. A large excess of zinc dust has been used without changing the yield.

2. Great care must be taken not to add too much zinc dust at first as the reaction becomes very vigorous. It is well to have a bath of ice and wet towels at hand in order to control the reaction if it should become too violent.

3. Occasionally the reaction suddenly stops and it is necessary to add an additional quantity of 10 cc. of 20 per cent sodium hydroxide solution, which causes the reaction to proceed.

4. The product can also be purified by distillation under reduced pressure in an inert atmosphere, but unless the material is very nearly pure, considerable decomposition occurs and the distilled product darkens rapidly in contact with air.

5. The free diamine may also be converted into the dihydrochloride, and the salt purified as follows: The crude *o*-phenylenediamine is dissolved in a mixture of 90–100 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 50–60 cc. of water containing 2–3 g. of stannous chloride, and the hot solution is treated with decolorizing charcoal. To the hot, colorless filtrate is added 150 cc. of concentrated hydrochloric acid, and the mixture is cooled thoroughly in an ice-salt bath. The colorless crystals are filtered by suction, washed with a small amount of cold concentrated hydrochloric acid, and dried in vacuum over solid sodium hydroxide. The yield of *o*-phenylenediamine dihydrochloride is

77–81 g. (85–90 per cent of the theoretical amount based on the weight of *o*-nitroaniline used).

3. Methods of Preparation

o-Phenylenediamine has been prepared by the reduction of *o*-nitroaniline by means of tin and hydrochloric acid,[1] stannous chloride and hydrochloric acid,[2] sodium stannite,[3] zinc dust and water,[4] sodium hydrosulfite and sodium hydroxide,[5] zinc dust and alcoholic alkali,[6] and by electrolytic reduction in aqueous alcohol in the presence of sodium acetate.[7] The present procedure is a modification of the method of Hinsberg and König.[6]

o-Phenylenediamine has been proposed as a reagent for the identification of aliphatic acids, by conversion to crystalline 2-alkylbenzimidazoles (p. 14).

[1] Zincke and Sintenis, Ber. **6**, 123 (1873); Koerner, Gazz. chim. ital. **4**, 320 (1874); Hübner, Ann. **209**, 361 (1881).

[2] Goldschmidt and Ingebrochtsen, Z. physik. Chem. **48**, 448 (1904); Goldschmidt and Sunde, ibid. **56**, 23 (1906).

[3] Goldschmidt and Eckardt, ibid. **56**, 400 (1906).

[4] Bamberger, Ber. **28**, 250 (1895).

[5] Borsche, Chem. Zentr. **80**, II, 1550 (1909).

[6] Hinsberg and König, Ber. **28**, 2947 (1895).

[7] Rohde, Z. Elektrochem. **7**, 339 (1900).

XXVI

PHENYLNITROMETHANE

$$C_6H_5CH_2CN + CH_3ONO_2 + NaOC_2H_5 \rightarrow \underset{\substack{|\\ CN}}{C_6H_5C{=}NO_2Na} + CH_3OH + C_2H_5OH$$

$$\underset{\substack{|\\ CN}}{C_6H_5C{=}NO_2Na} \xrightarrow[H_2O]{NaOH} \underset{\substack{|\\ CO_2Na}}{C_6H_5C{=}NO_2Na} \xrightarrow{HCl} C_6H_5CH{=}NO_2H + CO_2$$

$$C_6H_5CH{=}NO_2H \rightarrow C_6H_5CH_2NO_2$$

Submitted by ALVIN P. BLACK and FRANK H. BABERS.
Checked by JOHN R. JOHNSON and H. B. STEVENSON.

1. Procedure

(*A*) *Sodium Phenyl-aci-nitroacetonitrile.*—In a 2-l. round-bottomed flask fitted with an efficient reflux condenser is placed 400 cc. of absolute ethyl alcohol. Through the condenser tube 46 g. (2 gram atoms) of freshly cut metallic sodium is added as rapidly as possible, and the flask is heated in an oil bath after all the sodium has been added. After about one-half hour only a small globule of molten sodium (0.5–1.0 g.) remains and sodium ethoxide begins to precipitate. At this point 100 cc. of absolute alcohol is added and the mixture is cooled to 0°. A second 100-cc. portion of cold absolute alcohol is then poured on top of the solid cake of sodium ethoxide in the flask (Note 1). The reflux condenser is replaced by a stopper carrying a separatory funnel and a calcium chloride tube. An ice-cold mixture of 234 g. (2 moles) of freshly distilled benzyl cyanide (Org. Syn. Coll. Vol. **I**, 101; **16**, 89) and 216 g. (180 cc.; 2.8 moles) of methyl nitrate (Note 2) is added with constant shaking, at such

a rate that the temperature is kept between 4° and 8°. After this addition is completed (about one hour is required), the reaction mixture is allowed to remain at 4–8° and shaken intermittently for one hour. The flask is then provided with a stopper fitted with a Bunsen valve and placed in a freezing mixture for twenty-four hours. The sodium salt of the *aci*-nitro compound which precipitates is filtered with suction on a Büchner funnel, washed thoroughly with dry ether (Note 3), and air dried. The first crop of material weighs 215–275 g. (58–75 per cent of the theoretical amount). The mother liquor and ether washings are combined and concentrated stepwise to about 150 cc. under reduced pressure. Successive crops of the sodium salt which separate are filtered with suction and washed with dry ether. The total weight of the crude sodium salt is 275–300 g. (75–82 per cent yield). This material is used directly without purification.

(*B*) *Phenylnitromethane.* In a 4-l. beaker 300 g. of sodium hydroxide is dissolved in 1200 cc. of water. The beaker is placed in an enameled pan (as a precaution against breakage), and the solution is heated to boiling. Over a period of one hour the air-dried, crude sodium salt of phenylnitroacetonitrile (275–300 g.) is added in small portions to the boiling alkali. Boiling is continued until the evolution of ammonia ceases (about three hours); hot water is added from time to time to keep the volume of the solution fairly constant (Note 4). The hot alkaline solution is poured into a shallow porcelain dish and on cooling solidifies to a waxy mass.

The cake of crude sodium salt of phenylnitroacetic acid is broken up with a spoon, transferred to a 4-l. beaker, and stirred with 500 g. of ice. The beaker is placed in a large crock packed with ice-salt mixture, and is provided with a mechanical stirrer. When the solution in the beaker has cooled to −5°, concentrated hydrochloric acid is added slowly from a separatory funnel, with vigorous stirring, until the solution is faintly acid to Congo red. During the addition of acid the temperature is not allowed to rise above −5° (Note 5). Usually about 900 cc. of acid is needed and the addition requires about two hours. The

cold solution is extracted with one 500-cc. portion of ether, followed by two 250-cc. portions. The combined ether extracts are washed with ice-cold portions of saturated sodium bicarbonate solution until the wash liquid is colorless or only faintly yellow (usually two 100-cc. portions suffice). The ether solution is then washed with 250 cc. of ice water containing two drops of hydrochloric acid, and finally with three 50-cc. portions of ice water. The ether solution is dried over anhydrous sodium sulfate and allowed to stand for three or four days to complete the isomerization of the labile *aci*-form. The solution is filtered and the ether removed at 15–20° under reduced pressure. The residual oil is distilled at low pressure (3 mm. or less) in an ordinary Claisen flask, and the phenylnitromethane is obtained as a light yellow oil, b.p. 90–92°/3 mm. (Note 6). The yield is 135–150 g. (50–55 per cent of the theoretical amount, based upon the benzyl cyanide).

2. Notes

1. The supernatant layer of alcohol prevents the reactants dropping directly onto the sodium ethoxide and causing local overheating.

2. The large excess of methyl nitrate increases the yield appreciably. Freshly prepared methyl nitrate (p. 64) was dried and used directly without distillation. It is convenient to use the entire product (usually 210–230 g.) obtained from 120 g. of methyl alcohol.

3. Ordinary ether that has been allowed to stand for several days over anhydrous calcium chloride may be used.

4. The reaction must be watched carefully. Vigorous foaming sometimes occurs and necessitates the addition of small quantities of cold water from a wash bottle.

5. At −5° the *aci*-nitro compound separates as a gray, pasty solid. When the solution becomes acid the colloidal precipitate tends to undergo coagulation.

6. In the distillation of the crude product it is essential to maintain a low pressure and to avoid overheating. If the distillation is pushed too far, decomposition occurs and the distillate

discolors rapidly on standing. If the distillation is not carried out carefully violent decomposition may occur which will blow out all connections.

The distilled product decomposes on standing and should be used promptly. Phenylnitromethane should not be stored in a glass-stoppered bottle, as the stopper is likely to become frozen and explosions may occur in attempting to remove it.

3. Methods of Preparation

Phenylnitromethane has been prepared by the nitration of toluene with dilute nitric acid in a sealed tube,[1] by the interaction of benzenediazonium chloride and nitromethane in alkaline solution,[2] by the action of silver nitrite on benzyl chloride [3] or iodide,[4] and by the condensation of ethyl nitrate with benzyl cyanide and subsequent hydrolysis.[5] The use of methyl nitrate, which can be prepared with less danger and difficulty than ethyl nitrate, is advantageous.

[1] Konowalow, Ber. **28**, 1860 (1895).
[2] Bamberger, Schmidt and Levinstein, ibid. **33**, 2053 (1900).
[3] Hollemann, Rec. trav. chim. **13**, 405 (1894).
[4] Hantzsch and Schultze, Ber. **29**, 700 (1896).
[5] Wislicenus and Endres, ibid. **35**, 1755 (1902); cf. Gattermann-Wieland, "Laboratory Methods of Organic Chemistry," p. 256. Translated from the twenty-fourth German edition by W. McCartney, The Macmillan Company, New York, 1937.

XXVII

PHENYLPYRUVIC ACID

$$C_6H_5CH{=}C\begin{cases}NHCOCH_3\\CO_2H\end{cases} + H_2O + HCl \rightarrow$$
$$C_6H_5CH_2COCO_2H + CH_3CO_2H + NH_4Cl$$

Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

Ten grams (0.05 mole) of α-acetaminocinnamic acid (p. 1) and 200 cc. of 1 N hydrochloric acid (Note 1) are placed in a 500-cc. flask fitted to an upright condenser with a ground-glass joint. Hydrolysis is completed by boiling for three hours. A few droplets of pale green oil may separate from the boiling solution; these are removed by filtration. The crystals of phenylpyruvic acid which separate from the filtrate on cooling (Note 2) are transferred to a Büchner funnel and washed with a little ice-cold water. The combined filtrate and washings are extracted with four 50-cc. portions of ether. The solvent is removed from the ether solution by evaporation at room temperature, finally in a vacuum desiccator (Note 3). The residue is combined with the first crop of crystals and dried in a vacuum desiccator over calcium chloride and potassium hydroxide. The yield is 7.2–7.7 g. (88–94 per cent of the theoretical amount), and the product melts at 150–154° (Notes 4 and 5).

2. Notes

1. Larger quantities of phenylpyruvic acid may be prepared by increasing the amounts of reactants proportionately. However, this is advisable only when the product is to be used imme-

diately since phenylpyruvic acid begins to decompose after standing only a few days.

2. The amount of phenylpyruvic acid which separates from the filtrate is increased if the solution is allowed to stand in the refrigerator several days before filtration. No decomposition was noted when the product was kept suspended in cold, dilute acid.

3. The evaporation may be carried out conveniently at room temperature by passing a stream of dry air or inert gas over the surface of the solution under a glass bell.

4. The melting point varies considerably with the rate of heating.

5. Phenylpyruvic acid may be recrystallized from ethylene chloride, benzene, or chloroform, but losses due to instability of the compound are quite large.

3. Methods of Preparation

Phenylpyruvic acid has been prepared by the hydrolysis of α-benzoylaminocinnamic acid with alkalies or acids;[1,2] by the acid hydrolysis of ethyl phenyloxalacetate;[3] by the acid hydrolysis of ethyl phenylcyanopyruvate;[2,4] by dehydration of β-phenylglyceric acid with sulfuric acid;[5] by the alkaline hydrolysis of phenylethoxalylacetamide;[6] and by the alkaline hydrolysis of α-acetaminocinnamic acid.[7]

[1] Plöchl, Ber. **16**, 2817 (1883).
[2] Erlenmeyer, Jr., Ann. **271**, 165, 173 (1892).
[3] Wislicenus, Ber. **20**, 592 (1887).
[4] Erlenmeyer, Jr., and Arbenz, Ann. **333**, 228 (1904); Hemmerle, Ann. chim. (9) **7**, 229 (1917).
[5] Dieckmann, Ber. **43**, 1034 (1910).
[6] Bougault, J. pharm. chim. (7) **10**, 297 (1914).
[7] Bergmann and Stern, Ann. **448**, 27 (1926).

XXVIII

p-THIOCYANODIMETHYLANILINE

(*N*,*N*-Dimethyl-*p*-thiocyanoaniline)

$$C_6H_5N(CH_3)_2 + Br_2 + 2NH_4SCN \rightarrow 2NH_4Br + p\text{-}NCS{-}C_6H_4N(CH_3)_2 + HSCN$$

Submitted by R. Q. Brewster and Wesley Schroeder.
Checked by Wallace H. Carothers.

1. Procedure

A solution of 60.5 g. (0.5 mole) of dimethylaniline and 80 g. (1.05 moles) of ammonium thiocyanate in 250 cc. of glacial acetic acid, contained in a 1-l. beaker, is cooled to 10–20° in a bath of ice and water. The solution is stirred mechanically while a solution of 80 g. (0.5 mole) of bromine in 100 cc. of glacial acetic acid is added dropwise, over a period of twenty to thirty minutes, and the temperature is kept below 20° (Notes 1 and 2). After all the bromine has been added the reaction mixture is removed from the cooling bath, and after standing at room temperature for ten minutes is poured into 5–6 l. of water. Most of the *p*-thiocyanodimethylaniline separates as a pale yellow solid (Note 3), which is collected on a suction filter and washed with water. After drying in air it weighs 50–55 g. and melts at 71–73°. An additional 10–15 g. of less pure product is obtained by making the filtrate alkaline to litmus, which requires about 1250 cc. of 20 per cent sodium hydroxide. The two fractions are combined, dissolved in about 1200 cc. of boiling ligroin (b.p. 90–100°), and filtered rapidly through a large fluted filter in a heated funnel. The product separates from the filtrate in the form of long yellow needles, and crystallization is completed by thorough chilling. The melting point of the purified product is 73–74°,

and the total yield is 56–60 g. (63–67 per cent of the theoretical amount) (Note 4).

2. Notes

1. At higher temperatures a considerable quantity of a yellow thiocyanogen polymer is formed which contaminates the product.
2. Toward the end of the addition a heavy precipitate begins to accumulate on the walls of the beaker; this should be dislodged occasionally with a spatula.
3. *p*-Thiocyanodimethylaniline is a weak base and its salts are easily hydrolyzed.
4. An additional 4–5 g. of low-melting product may be recovered by evaporation of the mother liquor.

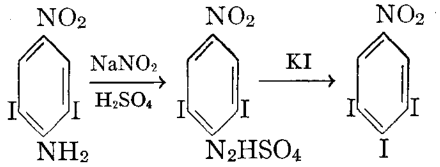
3. Methods of Preparation

p-Thiocyanodimethylaniline has been prepared by the action of thiocyanogen on an ethereal solution of dimethylaniline,[1] and also by the action of chlorothiocyanogen on dimethylaniline.[2] The procedure given above is a convenient method involving the formation of an active thiocyanogen derivative in the presence of dimethylaniline.[3,4] Thiocyanation of aromatic amines and phenols has also been accomplished electrochemically.[4,5]

[1] Soderbach, Ann. **419**, 275 (1919).
[2] Lecher and Joseph, Ber. **59**, 2603 (1926).
[3] Likhosherstov and Petrov, J. Gen. Chem. (U.S.S.R.) **3**, 183 (1933) [C. A. **28**, 1677 (1934)].
[4] Helwig, U. S. pat. 1,816,848 [C. A. **25**, 5355 (1931)].
[5] Fichter and Schönmann, Helv. Chim. Acta **19**, 1411 (1936).

XXIX

1,2,3-TRIIODO-5-NITROBENZENE



Submitted by R. B. Sandin and T. L. Cairns.
Checked by F. C. Whitmore and L. H. Sutherland

1. Procedure

Fifty grams (0.13 mole) of 2,6-diiodo-4-nitroaniline (Org. Syn. **12**, 28) is dissolved in 200 cc. of concentrated sulfuric acid (sp. gr. 1.84) in a 1-l. two- or three-necked flask provided with a mechanical stirrer. The solution is cooled to 5° in an ice-salt mixture, and to it is added with stirring a mixture of 100 cc. of concentrated sulfuric acid and 12 g. (0.17 mole) of sodium nitrite, also cooled to 5° (Note 1). To liberate nitrous acid from the nitrosylsulfuric acid, there is then added slowly from a separatory funnel, with rapid stirring, 200 cc. of 85 per cent phosphoric acid (151 cc. of U.S.P. phosphoric acid diluted to 200 cc.). During the addition the temperature is kept below 10°. The mixture is removed from the ice-salt bath and stirred until diazotization is complete (one to two hours) (Note 2). At the end of this time the solution is poured, with stirring, into 2 l. of a mixture of cracked ice and water in a 4-l. beaker. To destroy excess nitrous acid about 15 g. of urea is added in small portions, with stirring, as long as gas is produced. If the mixture is not clear it is filtered and then treated gradually with a solution of 30 g. (0.18 mole) of potassium iodide in 200 cc. of water. To complete the reaction the mixture is heated until no more gas is

evolved. Any free iodine is removed by sodium bisulfite, and the mixture is then filtered on a Büchner funnel, washed free from sulfuric acid and inorganic salts, pressed and sucked as dry as possible. The product is then air dried to constant weight. The yield of light brown, crude material, m.p. 160–162°, is 60–61 g. (94 per cent of the theoretical amount). The pure product can be obtained by dissolving the crude material in 200 cc. of boiling benzene, filtering, and cooling the filtrate to 10°. The yield of yellow crystals melting at 161–162° (uncorr.) is 40–42 g. (65–70 per cent recovery).

2. Notes

1. The sodium nitrite must be finely powdered and added slowly with vigorous stirring to the sulfuric acid, which is kept at 5° in an ice-salt mixture. The evolution of oxides of nitrogen during the addition of the nitrite must be avoided.

2. During this time the temperature of the mixture gradually rises to that of the room. When diazotization is complete a drop of the mixture will form a clear yellow solution if added to 10 cc. of cold water.

3. Methods of Preparation

1,2,3-Triiodo-5-nitrobenzene has been prepared by several workers[1,2,3] by the diazotization of 2,6-diiodo-4-nitroaniline (without the use of phosphoric acid) and subsequent treatment with potassium iodide. The present procedure is an example of a general method developed by Schoutissen[4] for diazotization of weakly basic amines, such as the 2,6–dihalogen derivatives of *p*-nitroaniline.

[1] Wilgerodt and Arnold, Ber. **34**, 3343 (1901).
[2] Kalb, Schweizer, Zellner, and Berthold, ibid. **59**, 1866 (1926).
[3] Harington and Barger, Biochem. J. **21**, 169 (1927).
[4] Schoutissen, J. Am. Chem. Soc. **55**, 4531 (1933).

XXX

TRIPHENYLMETHYLSODIUM

$$(C_6H_5)_3CCl + 2NaHg \rightarrow Na[C(C_6H_5)_3] + NaCl + 2Hg$$

Submitted by W. B. Renfrow, Jr., and C. R. Hauser.
Checked by Lee Irvin Smith and E. C. Ballard.

1. Procedure

A solution of 63 g. (0.226 mole) of pure triphenylchloromethane (Note 1) in 1500 cc. of pure anhydrous ether is prepared in a 2-l. bottle provided with a tight ground-glass stopper, and 2100 g. of freshly prepared 1 per cent sodium amalgam (0.9 gram atom of sodium) is added (Note 2). The stopper is greased with a small amount of Lubriseal and the bottle is stoppered tightly. The bottle is clamped firmly in a mechanical shaker and shaken vigorously. The reaction is strongly exothermic, and the bottle should be cooled with wet towels during the shaking operation. A persistent blood-red color develops rapidly, generally within ten minutes. After shaking for three hours *the bottle is cooled to room temperature,* removed from the shaker, and allowed to stand undisturbed until the sodium chloride has settled to the bottom.

The ether solution of triphenylmethylsodium is separated from the sodium chloride and amalgam by the following procedure. The stopper of the reaction bottle is removed and replaced immediately by a closely fitting two-holed cork carrying a short glass tube that protrudes about 1 cm. into the bottle, and a long tube bent into a U-shape. The short tube is connected through a drying train to a cylinder of nitrogen. One arm of the U-tube reaches to within about 4 cm. of the bottom of the bottle, and the other end extends just below the bottom of a two-holed cork

that is fitted tightly into a 2-l. Erlenmeyer flask. The latter is filled with nitrogen and serves as receiver for the decanted solution. The cork of the Erlenmeyer flask is provided with a short-stemmed separatory funnel which serves to release nitrogen during the decantation and may be used subsequently to introduce reactants (Note 3). The corks are sealed by a coating of paraffin-wax. The stopcock of the dropping funnel is opened slightly, and the ether solution of triphenylmethylsodium is forced slowly and steadily into the nitrogen-filled flask by means of a small pressure of nitrogen from the cylinder. With proper adjustment of the height of the glass tube above the surface of the sodium chloride and amalgam, it is possible to remove all but 50 to 75 cc. of the ether solution.

If a good grade of triphenylchloromethane and freshly prepared amalgam are used the yield of triphenylmethylsodium is almost quantitative. The solution may be analyzed approximately, as follows: A 50-cc. aliquot portion is allowed to flow into 25 cc. of water in a separatory funnel. The aqueous layer is drawn off and the ether solution washed with three 25-cc. portions of water. The aqueous solutions are combined, boiled to expel ether, and titrated with 0.2 *N* sulfuric acid, methyl red being used as indicator.

2. Notes

1. A good grade of triphenylchloromethane, m.p. 112–113°, should be used. The commercial product may be recrystallized conveniently from a mixture of five parts of ligroin (b.p. 90–110°) and one part of acetyl chloride, using about 1.8 g. of solvent per gram of material.

2. A 1 per cent sodium amalgam is prepared by cutting 21 g. (0.9 gram atom) of sodium into pieces about 5 mm. square and dissolving them, one at a time, in 2100 g. of purified mercury. A piece of sodium is speared on the sharpened end of a long glass rod and thrust quickly beneath the surface of the mercury, in a 500-cc. wide-mouthed Erlenmeyer flask. To avoid damage from flying pieces of sodium resulting from the vigorous reaction, the glass rod is inserted through a piece of heavy cardboard which serves to cover the mouth of the flask during the reaction.

Sodium amalgam may be prepared also by the careful addition of pure mercury to molten sodium covered with toluene, preferably in a Kjeldahl flask (Org. Syn. Coll. Vol. **I**, 539, Note 1).

3. Triphenylmethylsodium is a useful reagent for the preparation of the sodium derivatives of very weak acids (aliphatic esters, acid anhydrides, etc.). An example of this procedure, using ethyl *iso*-butyrate, is given on page 43.

3. Method of Preparation

The procedure described above is a modification of the method of Schlenk and Ochs.[1]

[1] Schlenk and Ochs, Ber. **49**, 608 (1916).

ADDITIONS AND CORRECTIONS FOR PRECEDING VOLUMES*

(The numbers in parentheses following the name of the compound refer to the volume and page of Organic Syntheses. New methods or changes in procedure have not been checked unless otherwise noted.)

m-Bromobenzaldehyde (13, 30):

The procedure described in Note 6 gives a product that may contain more than 20 per cent of *m*-chlorobenzaldehyde. This contamination can be avoided by using stannous bromide instead of the chloride as the reducing agent.

A solution of stannous bromide is prepared by heating 119 g. (1 gram atom) of mossy tin with 705 g. (4 moles) of 46 per cent hydrobromic acid for two hours on a steam bath, with mechanical stirring. The solution is cooled to 40°, and 50 g. (0.33 mole) of *m*-nitrobenzaldehyde is added in one portion, with continued stirring. The temperature rises from the heat of reaction and finally reaches about 105°. After heating for one-half hour longer on a steam bath, the reaction mixture is cooled to 0° and the aminobenzaldehyde diazotized by the gradual addition of 23 g. (0.33 mole) of sodium nitrite in 75 cc. of water. The diazonium solution is poured into a hot suspension of cuprous bromide (prepared as described in Note 6), 100 cc. of 46 per cent hydrobromic acid is added, with stirring, and the mixture allowed to stand overnight. The mixture is steam-distilled and the *m*-bromobenzaldehyde isolated by ether extraction and vacuum distillation; b.p. 90–92°/4 mm. The yield is 41 g. (67 per cent of the theoretical).

F. T. Tyson, private communication.

* The usual section devoted to later references to preparations in the preceding volumes has been omitted from the present volume. This material will be included in Collective Volume II, covering Volumes X–XIX, which is scheduled to appear in 1942.

2-Carbethoxycyclopentanone (17, 30):

Reference was omitted to the elegant modification of Dieckman's method described by Linstead and Mead, J. Chem. Soc. **1934**, 940. The procedure is simple and is reported to give consistently high yields (86–90 per cent).

S. Krishnamurthy, private communication.

Chelidonic Acid (17, 40):

The product named ethyl chelidonate on page 41, line 17, is actually acetonedioxalic ester [$CO(CH_2COCO_2C_2H_5)_2$], since cyclization does not occur until the subsequent operation. The equation at the top of page 40 should be modified accordingly.

Harold King, private communication.

Coupling of o-Tolidine and Chicago Acid (16, 12):

One sample of technical Chicago acid contained so much of the impurity giving rise to the red dye that the removal of this dye by resalting presented considerable difficulty. Contrary to the statement of Note 9, it was found very advantageous in this case to purify the starting material. Seven hundred grams of a Chicago acid paste found by titration to contain 26.6 per cent of 1-amino-8-naphthol-2,4-disulfonic acid was dissolved by heating in 2 l. of water, the solution was filtered, heated to 70°, and salted out by the addition of sodium chloride (600–650 g.) until a thick paste was obtained. The precipitate was collected at 40°, pressed well by means of a rubber dam, dissolved in 2 l. of water, and resalted exactly as before. After drying for thirty-six hours in a vacuum oven at 75°, the nearly white product weighed 150–155 g. and contained 78 per cent of active reagent. The dye ("Tolidine-1824") obtained from this material showed no red impurity in the capillary test after the second salting.

L. F. Fieser and M. E. Gross, private communication.

Cyclohexyl Bromide (15, 26):

Cyclohexyl and cyclopentyl bromides may be prepared conveniently by simple modifications of the general procedure using hydrobromic-sulfuric acid (Org. Syn. Coll. Vol. I, 26).

A mixture of 100 g. (104 cc., 1 mole) of pure cyclohexanol (b.p. 159–160°) and 370 cc. of the hydrobromic-sulfuric acid solution (3 moles of hydrobromic acid, 1.5 moles of sulfuric acid) is allowed to stand overnight and then heated for one-half hour on a steam bath. The bromide layer is separated and washed with cold 85 per cent sulfuric acid (five volumes of concentrated acid diluted with one volume of water), followed by sodium carbonate solution and water. After drying over calcium chloride the product is distilled under reduced pressure (b.p. 63–65°/25 mm.; n_D^{20} 1.4936). The yield is 130–132 g. (80–82 per cent of the theoretical).

Cyclopentyl bromide was prepared in the same way from 86 g. (1 mole) of pure cyclopentanol (b.p. 139–140°) and 430 cc. of the hydrobromic-sulfuric acid mixture (1.75 moles hydrobromic acid, 3.5 moles sulfuric acid). The product distilled at 75–78°/120 mm. (n_D^{20} 1.4900) and weighed 133 g. (89 per cent yield).

OLIVER GRUMMITT, private communication.

Diazomethane (15, 3):

Attention is again directed to Note 6, warning against the toxic effects of this substance. A severe case of diazomethane poisoning has been reported by SUNDERMAN, CONNOR and FIELDS, Am. J. Med. Sci. 195, 469 (1938).

Phenoxthin (18, 64):

The boiling range recorded at the bottom of page 64 should read: 140–160°/5 mm.

SUBJECT INDEX

(This Cumulative Index Comprises Material from Volumes X through XIX of this Series; for Previous Volumes see Collective Volume I.)

(Names in small capital letters refer to the titles of preparations which are given in full detail. A number in ordinary bold-face type denotes the volume. A number in bold-face italics refers to a page which gives preparative directions for a substance formed either as principal product or as a by-product, or to a product which has been prepared by a method analogous to the one given. Other numbers in ordinary type indicate pages on which a compound is mentioned incidentally or information is given concerning an item other than a compound.)

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